Full Proposal form NWA-ORC 2022 - Form for Impact Plan Approach

HOLLAND HYBRID HEART

combining tissue engineering and soft robotics to build a biocompatible artificial heart that offers a future to heart failure patients

Holland
Hybrid
Heart

Table of Contents

1 Overview

1.1 Title

HOLLAND HYBRID HEART, combining tissue engineering and soft robotics to build a biocompatible artificial heart that offers a future to heart failure patients

1.2 NWA route(s) & cluster question(s)

Primary NWA route applicable to the research proposal*	*Regenerative medicine: game changer moving to broad areas of application*
Secondary NWA route(s) applicable to the research proposal (if applicable)	*Materials – Made in Holland* *Healthcare research, sickness prevention and treatment* *Personalized Medicine*
Primary cluster question applicable to the research proposal**	121. Can we design electronic or bio-electronic systems that communicate directly with our bodies as well as materials and technology that restore or support human body function?
Secondary cluster question(s) applicable to the research proposal (if applicable)	120. Can we design smart materials and structures that have new and advanced properties? 100. How can we use cells, stem cells, and biomaterials to engineer and regenerate tissues and organs? 88. How can we predict, prevent, and treat cardiovascular diseases (e.g., heart failure and thrombosis) in individuals at an early stage? 94. How do we improve the quality of healthcare while keeping it affordable? And how can technology aid in this process?

1.3 Schematic overview of consortium

	Main applicant			
	First name, surname, title(s)	***Organisation***	***Position***	***Expertise (in key words)***
1.	Jolanda Kluin, prof. dr.	Erasmus MC, Rotterdam	Cardiac surgeon, professor, head of the department	Cardiac surgery, tissue engineering, device development, soft robotics, virtual reality

no	**Co-applicant(s)**				
	First name, surname, title(s)	***Organisation***	***Host country***	***Position***	***Expertise (in key words)***
1.	Carlijn Bouten, prof. dr.	Eindhoven University of Technology	NL	Professor Cell-Matrix Interactions in Cardiovascular Regeneration, and head of the research group 'Soft Tissue Engineering & Mechanobiology'	*In situ* tissue engineering, cardiovascular tissue, heart valves, cell-material interaction, engineered tissue models
2.	Frans van de Vosse, prof. dr.	Eindhoven University of Technology	NL	Professor Cardiovascular Biomechanics	Evaluation of medical devices, computational modelling,

					experimental verification, clinical validation
3.	Bas Overvelde, dr. ir.	AMOLF & Eindhoven University of Technology	NL	Scientific Group Leader & Associate Professor	Soft robotics, designer materials, embodied mechanical/fluidic intelligence, design optimisation
4.	Arie Paul van den Beukel, dr.	Saxion University of Applied Sciences, Industrial Design	NL	UAS Professor of Industrial Design, Leader applied design research & FabLab	Industrial design, human centered design, ethics, application of design research methodologies, stakeholder analysis, co-design, technology assessment and valorization, technology development to support surgery preparation
5.	Ali Sadeghi, dr.	University of Twente	NL	Assistant Professor	Soft robotics, 3D weaving/printing, soft sensing integrated actuation, multi material & rubber 3D printing
6.	Mathias Peirlinck, dr.ir.	TU Delft	NL	Assistant Professor	Soft tissue biomechanics, computational biophysics, in silico modelling of soft organs and medical devices, machine learning, data-driven modelling
7.	Abeje Mersha, dr. ir.	Saxion University of Applied Sciences, Mechatronics	NL	UAS Professor of Mechatronics	Mechatronics, design, modeling and optimization of human-physical models in mechatronic applications and robotics, control technology, systems engineering. Co-founder of the Smart Industry Field Lab TValley
8.	Jan Mahy, dr.	Saxion University of Applied Sciences, Sustainable & Functional Textiles	NL	UAS Professor of Sustainable & Functional Textiles	Sustainable & functional textile research, industrial product development, yarn development, thin layer research, composites, coatings,

					technical textiles, smart textiles
9.	Rudolf de Boer, prof. dr.	Erasmus MC	NL	Cardiologist, professor, head of the department, president elect Dutch Cardiac Society (NVVC)	Clinical, experimental and translational cardiology, focus on heart failure, genetic heart diseases and cardio-oncology
10.	Kevin Veen, dr.	Erasmus MC	NL	Assistant Professor	Outcome research, predictive outcome modelling, systematic reviews, meta-analyses, health technology assessment, big data
11.	Eliza Bottenberg, dr.	Saxion University of Applied Sciences	NL	Senior researcher	Technical textiles, smart textiles, prototyping, textile production technologies, textiles for healthcare innovations, 3D weaving/knitting, soft robotics, body signal measurements, e-textiles, textile sensors
12.	Rogier Veltrop, dr.	Maastricht University	NL	Cardiovascular researcher	Patient perspective, patient advocacy, questionnaires, focus groups, molecular mechanisms in cardiac disease
13.	Herman van der Kooij, prof. dr.	University of Twente	NL	Professor Biomechatronics and Rehabilitation Technology	Design of mechanically-based medical devices

	Co-funder(s)					
	First name, surname, title(s)	*Organisation*	*Host country*	*Type*	*Sector*	*Expertise (in key words)*
1.	Jonne Hos	Dutch Heart Foundation (NHS)	NL	Foundation	Healthcare	Cardiovascular care, patient advocate
2.	Martin van Dijken, Wiro van Schaik	TrailBlazers	NL	Business SME	Service industry	Software development, organizational governance, device-patient interface, patient and relative advocacy
3.	Marc Evers, drs.	EE labels	NL	Business SME	Industry	3D weaving, smart materials

4.	Andreas Henseler, dr. ing.	Evos GmbH	DE	Business SME	Service industry	Development of medical devices, risk management, product verification, manufacturing process validation, regulatory approval, quality management system
5.	Jan Rietsema, dr.	Stichting Smart Biomaterials Consortium (SBMC)	NL	Business SME	Healthcare	(Bio)polymer materials, modification of biomaterials, processing of biopolymers and ceramics, analysis of cell-biomaterial interaction, up-scaling and automation of production processes, GMP
6	Jolien Roos, prof. dr.	Dutch Cardiovascular Alliance (DCVA)	NL	Foundation	Alliance	Research policies designed to maximise impact, implementation of solutions at hospitals, nurturing cardiovascular researchers, building data infrastructure, clinical trials & biobank

No	**Cooperation partner(s)**					
	First name, surname, title(s)	***Organisation***	***Host country***	***Type***	***Sector***	***Expertise (in key words)***
1.	Suzanne Streefland	Freelance	NL	Business enterprise	Radio and television broadcaster	Several editor and director positions at Dutch radio and television. Researches and reports on business, technology and innovation
2.	Inge Schalkers, dr.	Harteraad	NL	Association (ANBI)	Consultancy	Center of expertise for living with cardiovascular conditions. Practical, social and emotional support for patients with heart disease and their relatives

3.	Louise Bouman	Dutch Pulmonary Hypertenstion Association (PHA)	NL	Non-profit foundation (ANBI)	Public benefit institute	Representatives of Dutch patients with pulmonary hypertension and their relatives, promotes medical research, care, generating awareness for pulmonary hypertension, facilitates patient contacts

2 Problem analysis & Impact

2.1 Fit to NWA route(s) & cluster question(s)

Holland Hybrid Heart (HHH) addresses the following routes and questions:

1. HHH is at the heart of the NWA route **Regenerative Medicine: game changer moving to broad areas of application**, and particularly contributes to the questions: *Can we design (bio)electronic systems that communicate with our bodies as well as materials and technology that restore and support human body function (#121)? and How can we use cells, stem cells, and biomaterials to engineer and regenerate tissues and organs (#100)?* HHH not only combines natural and synthetic material concepts to create a soft bionic implant to functionally recover cardiac contractile function, it also advances the knowledge on how to recruit endogenous cells from the patient's blood stream to form a continuum with the patient's own living cells on the inside of the HHH, thereby allowing seamless integration in the human body and avoiding adverse haematological (thrombosis and bleeding) and immunological (rejection) reactions and minimizing biocompatibility issues.
2. HHH will strongly impact the NWA route **Materials – made in Holland** as it will provide novel concepts and tools for on-demand fabricating and testing of smart designer materials, while also showcasing the possibility of using mechanical and embodied intelligence directly in complex soft robotic constructs for organ function replacement, entirely made in Holland! The specific question of this route: *Can we design smart materials and structures that have new and advanced properties (#120)?* is therefore obviously key to this HHH proposal.
3. The scientific breakthroughs in HHH will bring better understanding of the functional restoration and treatment of the heart and will lay scientific foundations for better treatment strategies of HF using novel, hybrid implants. A such, HHH closely links to the route **Healthcare research, sickness prevention and treatment** and relates to the question: *How can we predict, prevent, and treat cardiovascular diseases (e.g., heart failure and thrombosis) in individuals at an early stage (#88)?* In addition, by replacing expensive, long-term care processes with HHH treatment, the project has the potential to provide a future answer to one of the grand societal challenges: *How do we improve the quality of healthcare while keeping it affordable? And how can technology aid in this process (#94)?*
4. HHH also links to the overarching route of **Personalized Medicine**. Individual sizing and shaping of HHH, as well as the adaptive, sensing material-designs and feedback loops, allow for revolutionary new concepts, enabling real-time and passive adjustment of cardiac function in line with patient specific physiological needs.

2.2 Suitability of Impact Plan approach

Our main aim is to develop a viable solution for advanced heart failure (HF) patients, that provides a considerably higher life expectancy and quality of life compared to the treatment options currently on the market. Given the clear goal for societal impact, **the Impact Plan approach** fits our project best. Importantly, the technology that we will develop to restore and support human body function *(question #121)* by using smart materials and structures that have new and advanced properties *(question #120)*, needs to be accepted and trusted by patients and their doctors in order to reach convincing societal impact. Moreover, such a device can only realistically reach societal impact when being brought to the market to achieve a return of investment for companies. Therefore, on the route to impact, next to the scientific team, patients, patient organizations, clinicians, ethicists, regulatory experts, medical insurance companies and business developers are involved from an early stage onwards. This to consider any developed innovation from a societal, industrial and economic point of view.

2.3 Societal & scientific impact

Long-term vision of the project

We envision the treatment of patients with heart failure (HF) in such a way that the survival and quality of life of HF patients drastically increases. We aim to achieve this by developing a unique bioinspired total artificial heart that integrates soft robotics and tissue engineering (TE) (Fig. 2.3.1). In the long term, we foresee that this pioneering technology allows us to **develop and bring to the clinic a full set of artificial motile organs and tissues that seamlessly integrate with the human body**. This will be possible as the novel and exciting technologies underlying the artificial heart developed in this project - **soft robotics and *in situ* TE** - can be used to generate a broad range of artificial motile organs such as muscle structures (e.g., limbs), bowels or lungs:

- The motility and flexibility in shape and size of soft robots[1–3] make them suitable for mimicking motile organs. Actuators can be embedded within the elastomeric matrix of these robots without compromising their malleable properties. In addition, embodied intelligence provides direct feedback on shape and force, enabling natural behaviour.
- Biocompatibility of these artificial organs is provided by TE inside the body (*in situ*) using biodegradable coatings or scaffolds[4]. Such TE scaffolds are cell-free synthetic bio-resorbable implants or linings that can recruit or interact with cells from the bloodstream, leading to gradual replacement of the scaffold by fully endogenous, and thus biocompatible, tissue. Importantly, the cell-free and thus off-the-shelf availability of these scaffolds avoids the high costs and complex logistics inherent to pre-implantation *in vitro* TE[5].

The Holland Hybrid Heart (HHH) consortium will push the development of these newly emerging technologies forward and combines soft robotics and *in situ* TE **to generate the first biocompatible, soft actuated heart.** This project will deliver Proof-of-Principle for full *in vivo* cardiac functionality of the artificial HHH in large animals. If successful, the HHH will be available for translation to the clinic as an effective treatment for advanced HF in patients and a valid alternative for moderately effective current HF therapies. This is a quantum leap forward in the treatment of HF.

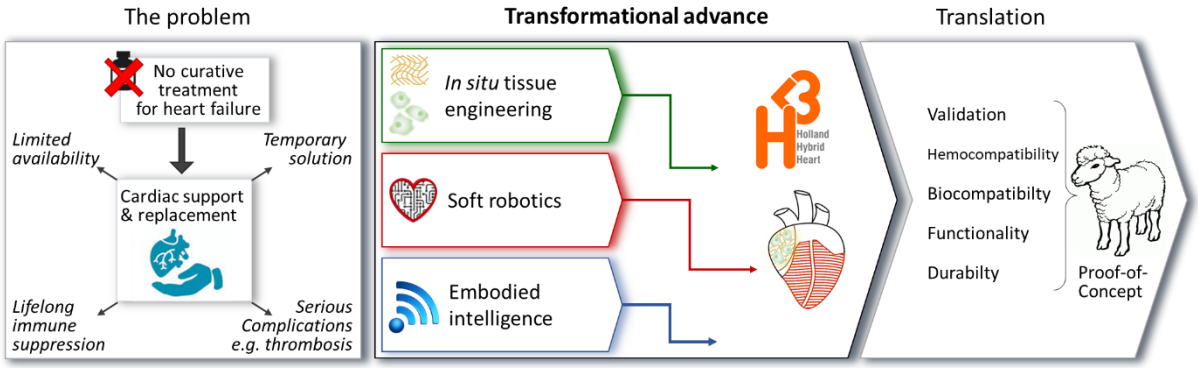

Figure 2.3.1. *HHH Project.*

The Proof-of-Concept obtained in the HHH project will be the stepping stone for development of other artificial motile organs. By providing an affordable and revolutionary effective alternative to human donor organ and tissue transplantation, HHH represents the future of organ replacement. As such, this project displays **a novel and radical long-term vision of a science- and technology-enabled future in medicine that is far beyond the state of the art and not currently foreseen by technology roadmaps.**

Societal Impact (see also Annex 1A)

Improved life expectancy & quality-of-life for HF patients

Developing the HHH as off-the-shelf available and scalable therapy to improve life expectancy and quality of life of patients with advanced HF

If successful, the HHH will be a solution for the many patients with advanced HF (including children and women) that are on waiting lists for donor hearts but face poor prognosis due to the limited availability of donor hearts. The HHH will have direct impact on patients for whom heart replacement is the final remaining option to survive and who otherwise die while waiting for a donor heart; the HHH will add additional high quality life years that patients can spend with their families. In addition, HHH will offer a treatment option to those patients who are not found eligible for heart transplantation (due to age, comorbidities, previous surgeries etc.) and to patients who are not yet in end-stage HF but have a low quality of life. Furthermore, HHH will offer an improved quality of life as compared to the quality of life that current rigid total artificial hearts and mechanical circulatory support devices (MCSDs) give. The clinical burden of HF on society is large (see section 2.4). By offering an alternative option for replacing failing hearts, the HHH has the potential to circumvent the dependency on donor hearts, avoid waiting lists, improve quality of life and reduce the clinical burden of advanced HF on society. In addition, if successful in treating advanced HF, the HHH is also beneficial for other patient groups like those suffering from pulmonary hypertension, widening the clinical potential.

Strengthened competitiveness and leadership of NL in biotech, material science and deep tech innovative landscapes

Strengthening Dutch leadership in the early exploration of visionary, new and emerging technologies, beyond academic excellence and with global recognition

Commercial leadership: The HHH technology has the potential to disrupt the market for MCSDs and total artificial hearts, which is currently estimated to reach € 7.5 billion worldwide in 2028[6]. This market is growing rapidly, due to the rise in HF patients globally, but its growth is currently limited by the complications inherent to the use of MCSDs, such as thrombosis and bleeding. Based on the large unmet clinical need, disruptive technology and attractive market opportunity, HHH has the potential to be a highly successful startup 'unicorn' that attracts profits to the Netherlands, but also generates economic activity throughout the medtech ecosystem. The HHH will be positioned as "Made in the Netherlands", which translates into high quality and is another example for the innovative excellence of the Netherlands. In short, HHH can be a showpiece for Dutch medtech innovation sector.

Academic leadership: Proof-of-Principle for a soft actuated heart with *in situ* TE will corroborate the leading role of Erasmus MC and Eindhoven University of Technology in TE, particularly in the cardiovascular field. In addition, it will showcase the leading role of AMOLF, Saxion, University Twente, and Delft University in soft robotics and material research, and its applications in the field of medical research. This project will ensure that these Dutch partners maintain their current position at the forefront of their respective field of expertise. This project fosters their joint academic excellence and industrial leadership to translate this revolutionary concept into actual new emerging products and technologies.

Combined, the HHH project has the potential to increase attractiveness of the Netherlands as a whole for talented researchers, entrepreneurs and investors - strengthening its competitiveness as innovation hub in various disciplines.

Involving new high-potential actors such as young, both female and male, researchers and high-tech SMEs that may become the European scientific and technological leaders and innovators of the future

In all academic research groups collaborating in this project, young PIs (male and female) will be involved in leading and performing the research needed to develop the HHH. Successful completion of a prestigious NWA-ORC project will assist them in their career path to become scientific leaders in their field. In addition, the PIs of the different institutions have been granted important (personal) grants and will train and mentor PhD students and postdocs to become excellent young researchers. The consortium includes four high-tech SMEs (EE Labels, TrailBlazers, Evos, SBMC) that are leading in their respective field of expertise (3D weaving, software, risk management, product verification, manufacturing process validation, regulatory approval, Quality Management System).

Scientific Impact (see also Annex 1A)

Solutions for a broad spectrum of diseases and challenges in- and outside the medical field

Scientific, medical and industrial communities are better equipped to seek solutions for a broad spectrum of diseases and challenges in- and outside the medical field
The incorporation of artificial organs or body parts ('bionic man') has often been suggested, but not realized so far. Since this will be the first Proof-of-Principle for the exiting combination of soft robotics and TE, the HHH project will lay the foundation for a novel line of technology with plenty of new applications in- and outside medicine. Once a soft robot is capable of replacing a malfunctioning human heart, this type of soft robots can be adjusted to provide novel solutions for engineering either muscle structures (limbs) or other organs (e.g., bladder, bowel, lung). As such, this project will change the future of organ replacement, using the latest advancement and new applications of soft robotics and TE technologies, which will cause a foundational shift in transplantation research and medicine with unlimited availability of biocompatible and off-the-shelf solutions for patients. Outside the field of medicine, novel soft robots are being developed for highly dynamic tasks and environments, such as locomotion in rough and unknown terrain or gentle but robust grasping of unknown objects. The methods used to develop both soft actuators needed for the HHH, as well as proprioceptive sensors and other components, can be used in these environments as well, and will thus impact the rapidly evolving field of soft robotic applications.

2.4 Problem analysis: societal problem and causes

The societal problem: Annually 1400 patients with advanced HF do not receive optimal treatment and face poor prognosis in NL

HF is estimated to affect ~23 million patients worldwide[7], and in general, outcomes for people with HF are unacceptable and in advanced stages can be poorer than many forms of cancer[8]. Beyond the mortality risk, HF has a considerable and lasting impact on patient's health and wellbeing[9]. Aside from the medical burden of HF on society, the economic impact of HF on society is immense. The World Bank estimates the global direct and indirect costs associated with HF at $108 billion per year[4,5]. It is estimated that HF annually costs Dutch society €538 million.

For patients with advanced HF, the future is currently very uncertain. Current treatment options include intravenous drug support requiring hospitalization, implantation of a long-term mechanical circulatory support device (MCSD), or donor heart transplantation. Heart transplant currently remains the gold standard therapy for selected patients with advanced HF with annually ~2,000 transplants in Europe[10]. However, this preferred treatment is only accessible for a select group of patients. Only patients with a high chance of surviving the transplant procedure can join the waiting list. Still, waiting lists are very long, with +1100 patients on waiting list in EU in 2021 according to Eurotransplant. Between 2013-2017 only 50% of Dutch heart transplant candidates actually received a donor heart. Consequently, today 17-45% of advanced HF patients die within a year, and the vast majority does not survive for more than 5 years. The situation is even more distressing for paediatric patients and women, since the availability of young donor hearts is very limited while the dimensions of most MSCDs are not suitable for children or smaller women.

With drivers such as the ageing population and rise of first world diseases like diabetes and obesity that increase the risk of HF, the prevalence of HF is increasing at a rate of 2.2% each year[11]. At the same time, it is not expected that the availability of donor hearts will increase. Thus, there is an ***urgent*** unmet medical need for solutions that can improve the prognosis of patients with advanced HF. Without effective alternatives to the gold standard of donor heart transplant, waiting lists and mortality rates are bound to rise along with the clinical and economic costs that go with it.

The causes: A lack of donor hearts and suboptimal alternative treatments

Limited availability of donor hearts: Donor organ availability is very limited. Many HF patients stay on the intensive care unit desperately waiting for a donor heart, which will not reach most patients in time. For paediatric patients and their parents, the situation is even more distressing due to the lack of young donor hearts.

Suboptimal alternative treatments: For patients with advanced HF, alternative treatment options include intravenous support with inotropic drugs requiring hospitalization and implantation of a long-term MCSD.

MCSDs have now become a standard therapy, despite a high associated morbidity and mortality and poor quality of life[12]. The main complications of MCSDs are thrombosis and bleeding resulting in (severe) brain damage, and driveline infections[12,13]. Even without complications, the quality-of-life following MCSD implantation is limited. For instance, only 8% of patients who have received MSCDs return to work, patients cannot take a normal shower or a bath. The situation is even more distressing for paediatric patients and women, since the dimensions of most MSCDs are not suitable for most children and smaller women. Women comprise a larger proportion of the prevalent HF population and have a higher incidence of HF relative to men. Moreover, roughly 55% of the total cardiovascular mortality in women is attributed to HF. Still, females are selected less compared to males for MCSD therapy, mainly because the devices do not fit the smaller female body. End-stage pulmonary hypertension patients form another patient group suffering from lack of treatment options. The right ventricle of the heart fails due to high pressures in the pulmonary circulation. These patients have high mortality risks, with a 3-year survival of 55 %[14]. They need a highly tailored and strong right ventricle, to compensate for the high pressures in the pulmonary circulation. Donor hearts nor current MCSDs can deliver this.

Briefly, the two state-of-the-art types of MCSDs are **left ventricular assist devices (LVADs)** and **Total Artificial Hearts (TAHs)**[15]**. LVADs** are implanted in patients with left ventricular failure and FDA approved to use as 1) bridge to transplant for patients that are on the waiting list to receive a donor heart; 2) destination therapy for patients that have no prospect of receiving a donor heart, to improve survival. Although LVADs have become a standard therapy, the risk and burden of adverse events associated with its use remain significant[16]. Adverse clinical outcomes such as brain damage due to thrombosis or bleeding, and driveline infections, result in a poor quality of life. Ventricular assist devices used as biventricular support (BiVADS) have even worse results with a survival rate of less than 50% after 1 year and very low quality of life. **TAHs** are MCSDs that replace both the right and left native ventricles and valves of the failing human heart. Currently, there are only two TAHs available: the SynCardia and CARMAT artificial hearts:

The **SynCardia artificial heart (https://syncardia.com/) is the only FDA approved TAH and benchmark competitor of the HHH**. The SynCardia is used in end-stage biventricular HF as a bridge to heart transplantation. So far, approximately 1,700 SynCardia implants have been performed, with several patients supported on the device for more than 4.5 years. Although these results are promising, the SynCardia is not suitable as a permanent solution because of its bulkiness, percutaneous drivelines and the large external controller leading to a **low quality of life**[17,18]. SynCardia continues clinical validation of its product with the ambition to apply the device as a destination therapy.

The **CARMAT artificial heart (https://www.carmatsa.com/en/)** is a hydraulic device currently being developed in France. It aims to promote biocompatibility and reduce thrombogenicity by making use of diaphragms and valves of bovine pericardium. It has been implanted in 19 patients so far, demonstrating a maximum duration of support of 270 days. The reported causes of death were mechanical failure, multi organ failure and respiratory failure. There were no thromboembolic complications observed[19]. Like the SynCardia, the device is bulky and needs a percutaneous driveline. CARMAT received CE marking for use as a bridge to transplant (reported Dec 2020), and aims to be the first TAH with regulatory approval as destination therapy. Though, at present, CARMAT implantations have been temporarily stopped due to too many fatal mechanical failures.

Knowledge-related causes: *Off-the-shelf, soft, synthetic artificial hearts* have the potential to overcome the shortage of donor hearts and the drawbacks of current rigid artificial hearts but several knowledge and technology gaps hamper progress:

What soft robotic design and what soft materials are able to sufficiently and durably mimic natural cardiac motion? The heart is an extremely intricate organ consisting of soft tissues with specific mechanical properties and fluid dynamics that enable its rhythmic pump function. Any deviations in the mechano-physiological properties can have detrimental effects. Any artificial replacement should mimic the mechano-physiological properties of the natural heart in order to achieve **natural cardiac motion.** This is required to maximize the chance of safe and effective replacement. Preliminary studies with soft direct cardiac compression devices, soft robotic matrices and 3D printing yielded important insights, and show encouraging results. However, so far,

despite these advances in soft robotics, no complete bio-inspired artificial heart has been developed and it remains to be discovered what the optimal combination of materials, design and fabrication is.

How can we prevent immunogenicity and thrombosis? One of the key challenges for an artificial heart to overcome relates to bio- and immune compatibility. An artificial heart, like any other implantable device, must avoid activation of the immune system. In addition, it must ensure that no blood coagulation (being the biggest problem with the current MCSDs) or other biocompatibility issues occur. So far, the best way to address this is unknown. Using soft materials holds great promise in this regard. Another promising option entails growing cells on the inside of the artificial heart (inner-lining). Preliminary data show that *in situ* TE technology involving a bio-resorbable synthetic scaffold to which endogenous cells adhere, can succeed in this. However, it remains to be studied to what extend this is effective in large animal models.

How can we realize software-guided dynamic regulation of heart rhythm? The electrical circuit of the heart is very complex and regulates heart rhythm dynamically, adjusting it to the body's needs. It is currently unknown how to optimally control and monitor motility to achieve the best results.

What unforeseen safety, practical and physiological issues arise upon translating such a technology to the clinic? Once the envisioned reality of a soft robotic TAH is tested in large animals and gets closer to clinical application, new safety, practical and physiological issues will arise that need addressing. These can only be identified (and addressed) by crossing 'the valley of death' and really taking this technology from bench to bed.

The HHH consortium contains all relevant expertise required to fill these knowledge gaps and pave the way for **the Holland Hybrid Heart**: the first off-the-shelf synthetic, soft-robotics and tissue engineering-based artificial heart (see section 4 for an overview of the consortium and the participant's complementary competencies).

Assumptions

Assumption 1: The supply of heart donors is not expected to increase, thus continues to be insufficient to address the clinical need.

Not tested in the project, but due to an increase in HF and a stable number of donor hearts over the years, the demand for donor hearts is expected to increase.

Assumption 2: Replacement of the heart is better than alternative existing or emerging treatment options.

Considering the donor waiting lists and high mortality rates, it is clear that existing therapies do not adequately improve outcomes of patients with advanced HF. Researchers and clinicians focus on four ways to improve survival and quality of life in HF patients: 1) expand donor heart availability by xenotransplantation or ex vivo treatment of unfit donor hearts, 2) (stem)cell/gene therapy to treat or cure HF, 3) TE of the whole heart or pieces of heart muscle, and 4) minimizing the size of MCSDs. So far, xenotransplantation, has unfortunately not been successful despite long-term efforts[20]. Very recently, the first clinical cardiac xenotransplantation has been performed. The donor heart only functioned for a couple of days and the patient passed away after 4 weeks[21]. Ex-vivo treatment of unfit donor hearts is in its infancy but will never lead to a relevant increase in donor hearts[16]. A very large number of cell/gene therapy studies have been performed but this has not resulted in any substantial improvement in prognosis or quality of life of patients with HF[22]. Back in 2020, researchers were able to TE a rat heart though with a contractile function of only 2% [23]. Since then, no progress at all has been achieved. Minimizing the size of MCSDs will enable implantation in smaller female and possibly even (the larger) paediatric patients. However, the complications such as bleeding, stroke and driveline infections will not be affected by the size of the device.

Within the project, our hybrid heart will be prototyped and validated in a large animal model. The results will give an indication of the feasibility of the ultimate clinical potential upon optimizing the technology. It will not become clear how our hybrid heart will hold up against future therapies such as cell-based or gene therapies, but it is expected that replacement of the heart with a soft, fully functional, physiologically similar robotic version will result in better outcomes (survival and quality of life) than any of the existing MCSDs, xenotransplants or TE attempts.

Assumption 3: It is assumed that upon having access to a soft robotic artificial heart, this will be adopted by clinicians, patients and citizens.

Ethics & acceptance: it is unclear to what extent citizens and in particular patients will embrace the idea of an artificial soft robotic heart, what barriers exist that limit acceptance, and what measures can be taken to minimize those barriers. This will be analysed and tested in the project. Because user acceptance is crucial, together with the Pulmonary Hypertension Association, we already have conducted a patient survey to assess technology acceptance and willingness of patients to engage in first clinical studies (see section 4).

3 Impact Pathway

3.1 Outcomes

Outcomes

1.1 Medical and industrial communities use parts of the HHH and/or other soft robotic organs for different indications and applications. The HHH project will lay the foundation for a novel line of technology with plenty of new applications in- and outside medicine. Biocompatible, off-the shelf artificial organs/body parts are available for patients, which will result in improved life expectancy/quality of life for many patients with different diseases and medical needs. As such, this project could change the future of organ replacement, using the latest advancement and new applications of soft robotics and TE technologies, which will cause a foundational shift in transplantation research and medicine with unlimited availability of biocompatible and off-the-shelf solutions for patients. This includes the use of single components of HHH such as valves, single artificial muscles or software-guided dynamic regulation of heart rhythm being used as separate treatment options for patients in need (e.g. valve replacement). Outside of the field of medicine, novel soft robots are being developed for highly dynamic tasks and environments, such as locomotion in rough and unknown terrain or gentle but robust grasping of unknown objects. The methods used to develop both soft actuators needed for the HHH, as well as proprioceptive sensors and other components, can be used in these environments as well, and will thus impact the rapidly evolving field of soft robotic applications.

1.2 Clinicians implant the HHH in patients with advanced HF. Upon successful (pre)clinical validation (showing the HHH is safe and effective) and certification, clinicians have access to, are allowed to, and are willing to include HHH in treatment plans. With each new case the body of evidence of safety and efficacy grows and clinicians will increasingly accept the HHH as an alternative to a donor heart. Ultimately, the HHH will be adopted in clinical guidelines.

1.3 'NewCo' commercializes HHH. Upon demonstrating safety and efficacy in good laboratory practice (GLP) animal studies and a first-in-human study, the spin-off company established in this project (referred to as 'NewCo') obtains endorsement for HHH from key opinion leaders, achieves regulatory approval, obtains reimbursement for HHH and secures additional funding. NewCo, tasked with continuing development and commercialization of the HHH, will enter the market (likely in collaboration with a distribution partner), upscale production and bring the HHH to clinics to be implanted in patients.

1.4 Regulatory authorities approve HHH for CE marking; health insurers reimburse HHH. In continuing the HHH development, a dossier with all relevant data (device specifications, preclinical and clinical results, full health technology assessment) convinces: 1) key opinion leaders that the therapy is safe, efficacious, and ethically justified - so they are willing to adopt it as a treatment option for their patients; 2) regulatory authorities to approve the HHH for use and registration as an active implantable class III medical device (outlined in the EU Medical Device Regulation (MDR) 2017/745, MHRA guidelines, MDCG guidelines, FDA guidelines and ISO standards); and 3) health insurers of the value of HHH in terms of patient outcomes and cost-effectiveness to reimburse the treatment.

Intermediate outcomes

2.1 Other scientific, medical and industrial communities take up the HHH core technologies and build upon it, researching and developing new applications. Effective collaboration between different fields, i.e. medicine, chemistry and physics, is essential to realise this, and the world leading partners of the HHH project join forces to reach this ambitious goal. Together, these researchers and clinicians ensure wide dissemination of their research results. Since both the topic of the project and the innovative technologies used are of interest to society at large, the consortium will ensure that information on the project is disseminated in a suitable form to all stakeholders and included a science journalist to the consortium.

2.2 HF Patients are asking for a HHH as treatment option. The acceptance of patients is crucial for the implementation and success of the HHH. Thus, patients and patient organizations are part of the HHH consortium and will be continuously involved to ensure the project evolves while keeping the patient's need the main focus. Additionally, the journalist Susanne Streefland will report on the HHH to keep the public informed.

2.3 Erasmus MC cardiac transplant teams are allowed and willing to implant the HHH in up to 10 patients as compassionate use. Prior to entering clinical trials, the team will supply the HHH as a non-complying medical device for the treatment of a Single Named Patient Human Device Exemption. This will provide the first initial clinical information in a handful of cases, building towards technical file submission and initiation of clinical trials towards CE marking and FDA registration. Further, this puts the Dutch health care system and especially the Erasmus MC in the leadership position regarding heart failure treatment.

Early outcomes

3.1 'NewCo' has first HHHs manufactured. Based on the design developed in this project, NewCo will outsource manufacturing of the HHH to a Dutch company (or if needed multiple companies with specific expertise on specific HHH components). The Dutch company (or companies) manufacture the different components and assemble the first HHHs to be used during the first-in-man study.

3.2 Investors finance Good Laboratory Practice (GLP) animal studies that result in approval for first-in-man studies. Main applicant Erasmus MC and the other consortium partners will prepare a development and exploitation plan to ensure the further development of HHH, and to facilitate clinical implementation of the HHH as soon as possible. Based on the investor-ready business plan and preclinical data, the spin-off company ('NewCo') will secure non-dilutive and dilutive funding to complete (pre)clinical development, registration and commercialization. Initially, investors will be attracted to finance activities up to the first technological milestone of demonstrating safety and efficacy in GLP animal studies, as required for approval for first-in-man studies.

3.3 Patients, relatives and clinicians get used to the idea of having a soft robotic total artificial heart. Tailored communication and involvement of stakeholders results in curiosity and acceptance of the idea of having a soft robotic heart.

Assumptions

Assumption 1: ***HHH will enter the market****:* As first step towards the market, the integrated HHH prototype developed within this project will be validated in sheep (WP5). The acute validation ensures fitting of the device and gives first indication about the requirements of the surgical procedure. The chronic validation will show that sheep can survive for 3 months with the HHH. This will be a massive breakthrough and huge step towards application in human. Further exploitation steps, such as the creation of a spin-off company with in-licensed IP, will be initiated during the project.

Assumption 2: ***Policy makers, clinicians and patients are accepting the HHH transplant; clinicians use it as a treatment and the HHH is reimbursed:*** As part of WP0, stakeholders such as patients, clinicians (cardiac surgeons, cardiologists, thrombosis and biocompatibility experts), ethicists, economists, and health insurance companies are involved to determine the requirements and identify driving factors for acceptance. To ensure their input, we included all stakeholders in the overarching WP0 and in our Advisory Board.

Assumption 3: ***HHH will be available for all HF patients:*** The HHH is an off-the shelf artificial heart, and is thus immediately available for all HF patients who currently are dependent on MCSD and/or are waiting for a donor heart. Further, the size of the HHH is adjustable, making it suitable for patients of all sizes including small women and paediatric patients. In addition, the power of the right ventricle can be increased to allow overcoming the high pulmonary pressures in patients with pulmonary hypertension.

Assumption 4: ***Scientists, medical and industrial communities will use the novel technical tools and knowledge to develop further bio-inspired artificial organs/body parts:*** There is a knowledge gap for the development of bio-inspired artificial organs/body parts and industrial soft robots, that the HHH project is able to fill. The communication strategy developed by the science journalist in the consortium will ensure dissemination to all potential stakeholders.

3.2 Output

Output 1: ***Ethical framework and set of requirements.*** The ethical framework holds insights in acceptance barriers for clinicians, patients, health insurance companies and citizens. Throughout the project, regular meetings (focus groups, interviews etc.) with all stakeholders will be organized as part of the overarching WP0 to assess HHH acceptance and define the set of requirements and boundary conditions. Furthermore, all stakeholders are represented in our Advisory Board. Finally, one patient (Rogier Veltrop) and one patient representative (Martin van Dijken) are member of the consortium and are in the lead of securing patient input. All stakeholders will be actively involved in shaping the HHH development to ensure that all their needs are met and the HHH will receive high acceptance once it is available to patients.

Output 2: ***Physiologically relevant soft robotic heart design.*** The contracting (pumping) functional components (soft robotic cardiac muscles) is the core of the HHH and are developed in WP1. We here build on earlier work and will also assess new designs. HHH prototypes are made and extensively tested (cardiac output, efficiency) in the Mockloop *in vitro* environment. Using computational modelling, the cardiac output under various physiological conditions is assessed. An essential part when developing the soft functional components is the material selection (durability) and manufacturing. Different fabrication techniques such as multi-material soft additive manufacturing, multi-step elastomer casting, computer-controlled textile fabrication and lamination, and in particular novel techniques in 3D weaving/printing to embed the soft sensor-integrated actuators into the soft matrix of HHH prototypes will be investigated.

Output 3: ***In situ tissue engineered biocompatible inner lining technology.*** The *in situ* TE biocompatible inner lining will consist of a bio- or topologically functionalized soft elastomeric surface that is initially cell-free (WP2). Upon receiving the HHH transplant, cells passing the material will attach (i.e., are recruited) to form a layer of the patient's own living cells (*in situ* TE inner lining). This inner lining will prevent adverse blood- and immune-related responses to the robotic heart, thus minimizing the risk of rejection and blood clots (thrombosis) - common challenges for cardiovascular implants. For its development, material scientists, tissue-, bio-, and immuno-engineers join forces and will design, fabricate and test materials for *in situ* TE inner lining as well as heart valves. This includes the generation of polymer scaffolds (e.g., via electrospinning) and/or coating with nano- or micro topologies (e.g. using nanoscribe or xolography), as well as computational modelling of thrombosis, and multiscale computational modeling of force and strain transmission.

Output 4: ***Software and hardware motility control.*** To be able to control HHH behaviour, a fluidic circuit is developed and soft sensing fibers are incorporated. Fluidic circuits will be used to transform a continuous inflow from a hydraulic pump into pulsating output that will activate the soft robotic muscles in the heart. The circuits will be designed to passively adapt to variations in the physiological conditions, without the direct need for electronic sensing. Besides passively controlling the heartbeat, we will incorporate soft sensing fibers within the soft matrix to monitor deformation and provide feedback to optimize motile behaviour. Various options to embody intelligence will be assessed.

Outcome 5: ***Spin-off company 'NewCo' with in-licensed IP and investor-ready business plan.*** The HHH consortium will establish a Dutch spin-off company (NewCo) that in-licenses the IP to the core technologies underlying the HHH, the results of the eHTA assessment, and the investor-ready business plan. NewCo develops a detailed business plan stating the most feasible business scenarios and strategies to secure funding to

continue further (pre)clinical development, first in man studies and lead further development and commercialization of the HHH, which is essential to reach the clinic.

Output 6: ***Manufacturing process of the integrated HHH.*** The components developed in output 2-4 will be integrated into one HHH, meeting the set of requirements and boundary conditions. This includes e.g., performance, durability, size and noise. Different prototypes are created to choose the best performing HHH in accordance with the set of requirements. Special attention will be paid to the durability and safety of the HHH.

Output 7: ***Integrated HHH prototype validated in sheep.*** Acute and chronic implementation of the HHH in the relevant large animal model demonstrate safety and performance.

Output 8: ***Early health technology assessment (eHTA).*** The established eHTA model provides information about target patient population(s) in a multi-stakeholder working group (including clinicians, patient representatives, ethicists and health economists/payer representatives), instruments to define clinical outcomes, quality of life and health care costs in the first-in-human trial and a cost-effectiveness model for HTA of the HHH versus the current HF treatment options.

Assumptions

Assumption 1: ***Stakeholders (patients, physicians, health insurance companies) will accept the HHH.***

We have joined forces with the Dutch advocacy group 'Dutch Heart Foundation (NHS)' (www.hartstichting.nl) and patient organisation 'Harteraad' (www.harteraad.nl), and have organized one face to face and two online meetings to guide the discussion between our scientific team and patients directly (Fig. 3.2.1). Four patients volunteered to read and review the full proposal. Early feedback from patients indicated that for patients, it is important to understand the ethical concerns associated with the HHH.

Figure 3.2.1. *Impression of meeting with stakeholders.*

Assumption 2: ***A soft robotic heart will closely mimic the human heart's physiology and anatomy.***

While radical, our ambition is not complete science fiction. With the Future and Emerging Technologies (FET) Open grant of €3 million, we started in 2018 with a small consortium to direct and explore the possibilities of our technology. Our recent results convince of the feasibility of bringing a soft robotics bioinspired heart to clinic. Now is the time to expand our scientific and translational efforts. By adding University Twente, Delft University and Saxion University of Applied Sciences to the FET-Open consortium (Erasmus MC, Amolf, Eindhoven University of Technology), the consortium has all the knowledge and manpower on board to develop, assess and build the HHH.

Assumption 3: ***The inner lining will prevent clotting and enhances biocompatibility.***

In the FET-Open project we explored the feasibility of adding an *in situ* TE lining to various soft materials. Based on our results thus far, we have confidence in achieving full hemo- and biocompatibility.

Assumption 4: ***The software and hardware motility control will allow for automatic adaption to the physical state of the patient (resting vs. exercising, embodied intelligence).***

This will be explored in the present project though we know from modern pacemakers that they are able to sense the physical state (walking, running, sleeping) of the patient. This technology in combination with soft materials that incorporate compliance by design, makes us feel confident that we can achieve passively and automatically controlled contractile behaviour.

Assumption 5: ***A fully integrated HHH will result in survival in sheep.***

This is a breakthrough step towards the clinic and will allow human clinical trials. Extensive *in vitro* Mockloop testing of the HHH will precede implantation in animals. The consortium is very experienced in performing large animal studies. The chronic animal studies will be executed at Medanex (Belgium), one of the two animal facilities in the world with an intensive care unit (ICU), experience with total artificial heart implantations and possibility to perform experiments under Good Laboratory Practice (GLP).

4 Consortium

The comprehensive HHH consortium is composed of complementary partners that together cover the **entire knowledge chain** needed to bring HHH to patients. The HHH consortium includes 15 partners: 1 university medical center (Erasmus MC), 3 universities of technology (UTwente, TU Delft, TU Eindhoven), 1 NWO institute (AMOLF), 1 university of applied sciences (Saxion), 4 R&D intensive SMEs (Trailblazers, EE labels, Evos, SBMC), 4 public benefit organizations working with and for patients (NHS, Harteraad, PHA, DCVA) and a freelance science journalist. We bring together medical, scientific, technical, computational, regulatory, economic and ethical expertise, as well as patients, patient representatives, relatives and patient organizations that voice the end-users.

Stakeholders: Below are the details of stakeholders involved in the consortium and other stakeholders who will be impacted by the HHH work. The consortium will jointly formulate and conduct the research and will work towards achieving scientific and societal impact.

Target group	Stakeholders within consortium	External stakeholders
Medical community	Cardiac surgeon, cardiologist (Erasmus MC), researchers in the field of tissue engineering (TU Eindhoven)	Professional organizations such as European Society of Cardiology, European Association of CardioThoracic Surgery, TERMIS
Soft robotic community	Researchers in UTwente, AMOLF, Saxion, TU Delft, Erasmus MC	Researchers and scientific organizations, such as IEEE Robotics & Automation, Dutch Soft Robotics
Medical device community	TU Eindhoven, EE labels, Evos GmbH	Companies interested in novel types of artificial organs or degradable materials, such as Abbott, Medtronic, Berlin Heart, Syncardia, Carmat, Straight Access Technologies, Xeltis.
Patient advocacy groups	Individual patients (Rogier Veltrop and Martin van Dijken), Dutch Heart Foundation (NHS), Maastricht University, Harteraad, Dutch Pulmonary Hypertension Association (PHA), Dutch Cardiovascular Alliance (DCVA)	International patient organizations for heart failure patients, patients that have a MCSD or underwent a heart transplant and patients with pulmonary hypertension
Regulatory bodies	Evos GmbH	Notified bodies, FDA, standardization institutes (ISO)
Healthcare payers	Health insurance company	Health insurance companies at national level
General public	Press: science journalist (Suzanne Streefland)	Dutch, European and global general public, governments

Co-design with stakeholders: Aside from all co-applicants and co-funders, patients, patient representatives and patient organizations have been engaged in the writing of this proposal. We have involved patients and patient organizations from the very early design of the project to ensure that the final design, medical procedures for implantation and follow-up ensure maximal patient benefit and comfort and thus maximal societal impact. **Examples of our current interactions** with patients and patient organizations are summarized below (non-exhaustive):

- **Two patients** (Rogier Veltrop and Martin van Dijken) **are consortium members.** They helped in writing the proposal and reviewed the text.
- **Meeting with patients:** We have joined forces with the Dutch advocacy group 'NHS' and patient organisation 'Harteraad' to organize one face to face and two online meetings to guide the discussion between our scientific team and patients directly. Four patients volunteered to read and review the full proposal. Early feedback from patients indicated that for patients it is important to understand the ethical concerns associated with the HHH.
- **Patient survey, 2021:** We collaborate with the Dutch Pulmonary Hypertension Association (PHA). We organized two patient sessions and conducted a survey in which 199 respondents participated. 100% of respondents evaluated HH development as 'very important' or important. 99% of respondents say that

they were 'very interested' or 'interested' in its development. 17% of patients said they would want it as soon as it was available, 14% when symptoms became difficult and 30% when symptoms became very difficult to live with, 39% said they would want it when it was their only chance of survival.

- **Global reach:** The HHH team reaches out to patients and stakeholders globally. Early discussions with Brigadier Parag A Deshmukh, a cardiothoracic surgeon in the Indian army has indicated the HHH solution is of particular importance in countries in which donor transplants are not an option due to religious beliefs.
- During work of the H2020 FET open project (awarded to Prof. Kluin, EMC), two patient representatives were appointed in the **Scientific Advisory Board**. The patient representatives act as ambassadors for the project and facilitate the communication with other stakeholders, including patient associations and advocacy groups. Last advisory meeting was held on October 11th 2022.

Co-creation with Stakeholders: As stakeholders play a crucial part in achieving societal impact, one of the key objectives of HHH project is to involve patients, patient representatives, relatives, patient organizations, and the general public from the earliest phases of the project.

A) Incorporation of users' requirements into HHH technology design: Patients, patient representatives, relatives, care-givers, patient organizations, and clinicians are the primary stakeholders of the project. We will involve them from the start of the project (WP0 is dedicated to this, see for more detail the WP description). For this work, a robust interaction between users and researchers will be fostered to adapt the design requirements of HHH technology to users' needs. Specialists from the UserEngagement & DesignThinking lab at Saxion will ensure optimal stakeholder engagement throughout the project. The cooperation of patients, patient representatives, relatives and patient organizations has been budgeted (15 sessions throughout the project) We will collect users' perspective on device requirements and specifications and users will have the opportunity to provide any feedback via written and oral communication at all times. These user requirements will be translated into system requirements and will be integrated with the overall system architecture. Through these actions we will identify the user requirements from start of the project and will understand in close collaboration with patient organizations, which factors drive stakeholders' acceptance.

B) Advisory Board: The HHH consortium will leverage its existing network and interaction with stakeholders to establish a formal external independent Advisory Board. The Advisory Board will consist of up to 6 international key opinion leaders with acknowledged reputations in the field of soft robotics, TE, ethics and medicine and include: prof. Gummert, prof. ten Cate and prof. Roche. Currently, already 5 patient representatives have been appointed: Martin van Dijken, Rogier Veltrop, and representatives of Harteraad (Inge Schalkers), Dutch Pulmonary Hypertension Association (Louise Bouman) and the Dutch Heart Foundation (Jonne Hos). Participation of patients and patient organizations is budgeted. Furthermore, regulatory experts and health insurance companies will complete the Advisory Board (for details of role of advisory board in consortium governance structure, see section 4.2).
The board will act as an independent body to evaluate progress during plenary project meetings and provide input on the project activities, including ethical and other considerations from a patient's perspective. In brief, the key responsibilities of the board include:

- Join and provide insights based on annually plenary update meetings. In addition, the representatives will be available ad-hoc to discuss topics raised. Topics such as the acceptance of the new technology, first target patient populations, care after implantation and ethical issues will be included.
- Provide feedback on the development of material for dissemination of project results. By providing end-user feedback, any online content and public press releases will be tailored to match the needs of patients.

C) Broader patient engagement activities during this project: We will further expand patient engagement through additional activities such as discussions of the project plans, outcomes and future direction with patients, their relatives and ambassadors. We will focus on discussing the ethical considerations and concerns and procedures for patient care, including aftercare. We will intensify interactions with other European patient organisations to reach out to a wider network of patients. The purpose is to disseminate project progress and collection of feedback via Q&A sessions. The second pillar in patient engagement

involves a media campaign, for which our journalist and communication expert Suzanne Streefland will develop content for joint newsletters with patient organisations.

Consortium members: The following crucial partners are part of the HHH consortium (Fig. 4.1.1)

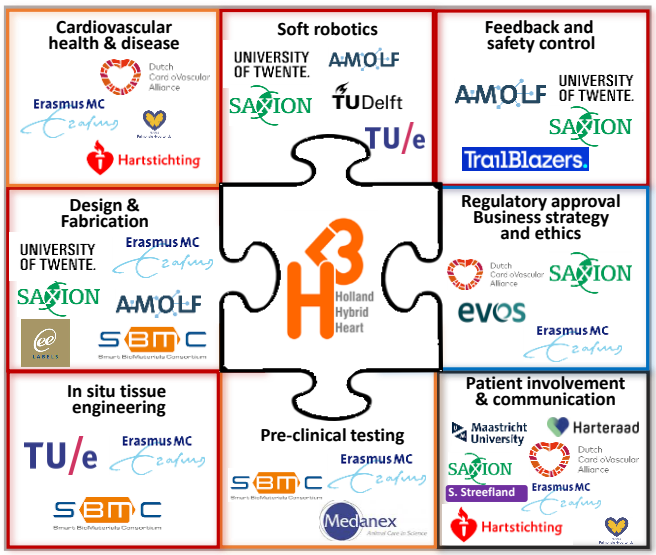

***Figure 4.1.1** Consortium members*

1. University Medical Centers (UMCs)

Applicant Erasmus UMC (EMC) is a prominent expertise center in heart failure treatment. It is the only center in the Netherlands that has all the relevant permits (heart transplantation for both adults and children and MCSD for both children and adults). **Prof. Jolanda Kluin** is head of the department of cardiothoracic surgery and a world-renowned expert in cardiac surgery and preclinical testing of new cardiac disease treatments. She is the PI of the FET-Open project in which she invented the soft robotic prototype for an artificial heart that forms the starting point for the current project. Moreover, she previously co-developed *in situ* TE valves together with Prof. Carlijn Bouten from TU/e. **Dr. Veen** is an assistant professor and specialized in IPD meta-analysis and health technology assessment. **Prof. Rudolf de Boer** is head of the department of cardiology and an expert in clinical and translational cardiology with the focus on heart failure. The experience of Prof. van Boer's group with clinical care and outpatient aftercare of patients with a MCSD or donor heart is important input to the project. Within this HHH project, EMC will be the coordinator of the consortium and will facilitate the collaborative research. Prof. Kluin will conduct the acute and chronic proof-of-concept experiments in large animal models by surgically implanting the HHH. Additionally, EMC's expertise in caring for HF patients (especially those on MCSDs or after a heart transplantation) will provide vital insights for the monitoring and decision-making protocols for HF patients.

2. Universities of Technology

Development of a soft robotic total artificial heart requires very specific knowledge and experience. A robust and complementary group of researchers from EMC, AMOLF, University Twente (UT), Delft University of Technology (TU Delft) Eindhoven University of Technology (TU/e) will focus on the development of the 'muscle', soft robotic, part of the HHH. **Prof. Carlijn Bouten** from the Biomedical Engineering department at TU/e is a frontier scientist in cardiovascular tissue engineering, focusing on material-driven *in situ* generation of living, autologous tissue. **Prof. Frans van de Vosse** from the Biomedical Engineering department of TU/e **and Dr. Mathias Peirlinck** from TU Delft have developed and applied computational models of living soft structures/organs and devices that can be used to optimize designs and eventually predict outcome of clinical application of the HHH given specific pathologies. EMC, AMOLF and TU/e have vast experience in *in vitro* verification of designs and performance assessment in Mockloop circuits. TU/e has implemented in silico and computational fluidic models in MCSDs. **Prof. Herman Kooij** from UT will play a key role in integrating all components to develop a biomedical device that can be successfully tested, where **dr. Ali Sadeghi** will use fiber reinforced 3D weaving/printing technology developed at UT, to fabricate the soft robotic heart 3D structure and integrate sensory fibers/fabrics that can be used to monitor deformation and guide optimization of the HHH design.

3. Universities of Applied Sciences

For the crucial step of overall system integration of HHH technologies, the close collaboration with applied researchers from co-applicant Saxion University of Applied Sciences (Saxion) is essential. Saxion is a hub with experts who will bring crucial knowledge, skills and expertise critical to HHH. **Dr. Jan Mahy** and **dr. Eliza**

Bottenberg, whose research group is the only technical textile research group in the Netherlands, will focus on optimizing the fabrication of the HHH prototype using sensorized textiles and 3D weaving and/or knitting techniques. **dr. Arie Paul van den Beukel's** Industrial Design research group will focus on the user/patient experience, ethics and requirements for the HHH device design. His UserEngagement & DesignThinking lab is very well equipped and specialized for this task. **Dr. Abeje Mersha's** Mechatronics research group is one of the leading applied research groups in developing innovative and smart mechatronics and robotics technologies using systems engineering approaches. In this project, his group focuses on novel control methodologies and overall integration the HHH technologies into a single device. Having all these relevant applied researchers, capacities, skills and infrastructure co-located at Saxion, ensures effective collaboration and it substantially improves the integration process, which is crucial for the success of the project.

4. Research Institutes and Knowledge Centers

Co-applicant AMOLF is leading in soft robotics, materials and physics and has worked previously on a soft cardiac simulator. **Dr. Bas Overvelde** is leading in embodying intelligence in soft robots by using fluidic circuits, smart structures with exotic mechanical behaviour, and design optimization. He has extensively collaborated with Prof. Jolanda Kluin in the FET-Open project on the mechanical testing of the initial soft robotic prototypes and has used fluidic circuits to replace electronics for controlling the beating behaviour of the first prototypes.

5. Industry and regulatory experts

The consortium includes four SMEs: EE Labels, TrailBlazers, Evos, SBMC (co-funders of this application) that are leading in their respective field of expertise (3D weaving, software, risk management, product verification, manufacturing process validation, regulatory approval, Quality Management System). **Marc Evers** as a co-funder (EE Labels) will help to develop the production of HHH in a robust industrialized manner. This will standardise the production of HHH and reduce variability arising from the handwork. **Martin van Dijken** from TrailBlazers, a NL based software development firm, will provide in-kind software development expertise as well as develop an insight platform. This platform will provide HHH-owners and medical staff with the necessary insights into the performance of the HHH and the health of the patient. **Dr. Andreas Henseler** from Evos GmbH, is an expert in technical development, regulatory, business affairs of medical device technology and has indispensable experience required for bringing HHH technology to the market. Co-funder **Dr. Jan Rietsema** is the director of Smart Biomaterials Consortium (SBMC), a business SME that offers high-quality facilities for industrialization of smart biomaterials and biodegradable implants used for regenerative medicine-based technologies. SBMC will contribute its knowledge and facilities to the realization of this project, especially in testing the usability and manufacturability of materials to be used.

6. Patients and patient organizations

The Dutch Heart Foundation **(NHS), Harteraad,** Dutch Pulmonary Hypertension Association **(PHA)** and Dutch CardioVascular Alliance **(DCVA)** have been involved in co-design and co-creation of this project proposal. **Rogier Veltrop,** a cardiovascular researcher from Maastricht University and **Martin van Dijken**, a software developer from Trailblazers are patient's advocates (a patient and patient representative respectively) and are important consortium members to include the patients' perspective.

7. Freelance journalist

To optimally disseminate the results of the project, a freelance science journalist, **Suzanne Streefland** is involved in the consortium as a cooperation partner. She is an experienced creator of scientific content for national radio and television in the Netherlands and will be involved in broadcasting the project results to the general public on Dutch television and radio.

8. Health insurance companies

Health insurance companies will be involved at the later stages of the project to provide advice on policy guidelines, users acceptance and costs related to healthcare insurance. They will serve in the Advisory Board of the HHH consortium. Budget for these consortium members is already allocated.

Complementarities in the expertise in the consortium: The uniqueness of the HHH consortium lies in the diverse and complementary background of the members: cardiac surgery and patient care, preclinical models, soft robotics, tissue engineering, computational modelling, medical device regulation, health economics, patient engagement, stakeholder analysis, ethical evaluation, social impact and medical technology, including training and entrepreneurship. Many partners are at the frontiers of at least two of the fields, helping to bridge them. The complementary expertise that will bring the HHH project to successful completion is listed in the table.

Expertise	Organizations
Cardiovascular health & disease	Erasmus MC, NHS, PHA, DCVA
Soft robotics	U Twente, TU Delft, AMOLF, TU Eindhoven, Saxion, Erasmus MC
Feedback & safety control	AMOLF, U Twente, Saxion, Trailblazers
Design & fabrication of HHH	Saxion, U Twente, AMOLF, Erasmus MC, EE labels
Software development	Saxion, Trailblazers, AMOLF, Evos
***In situ* TE**	TU Eindhoven, Erasmus MC
Pre-clinical testing	Erasmus MC, TU Eindhoven
Patient involvement and communication	DCVA, NHS, PHA, Harteraad, Saxion, U Maastricht, S. Streefland, Erasmus MC
Ethical aspects	Saxion, DCVA, NHS, PHA, Harteraad, Erasmus MC
Regulatory expertise	Evos, Erasmus MC

Benefit of the collaboration for achieving societal impact: Insights gained from studying the HHH prototypes – both in *in vitro* and in *in vivo* studies to provide information on the artificial heart's functionality, durability, biocompatibility and potential adverse events, as well as in microsimulation models to predict the effect of treatment on clinical outcomes, health-related quality of life, use of informal care and productivity – will have a huge impact on the currently available limited treatment options for patients suffering from advanced HF, and will give this patient group a new outlook on a life-saving treatment. Not only will this work provide a new treatment option, separate parts of the HHH can offer benefits to other patients as well (e.g., our work will yield new soft elastomeric heart valves that can be used as a more flexible, potentially durable and cost-effective alternative to the current prosthetic valves). In addition, by providing proof-of-concept for using scalable soft biocompatible artificial organs, the HHH consortium may revolutionize the field of transplantation medicine by providing the basis for artificial motile organs that seamlessly integrate into the body. These impacts would not be possible without the collaborative and integrated expertise of the members of the consortium.

4.1 Involvement and development of young and mid-level researchers within the project

Some young and mid-level researchers (Bas Overvelde from AMOLF, Matthias Peirlinck from TU Delft and Kevin Veen from Erasmus MC) already have leading positions in the HHH project. Furthermore, the PIs of the individual institutions will train and mentor PhD students and postdocs to become excellent young researchers. Placing young and mid-level researchers in leadership positions will contribute to the consolidation of their careers due to the experience, network and soft skills that they will acquire. The diverse and high-quality research environment that is created by bringing together the HHH consortium, creates an opportunity for growth of young and mid-level researchers. Furthermore, since this project will lead to major output (publications in peer-reviewed scientific journals, presentations at (inter)national conferences) this will positively influence their progress and visibility. Successful completion of a prestigious NWA-ORC project will assist them in their career path to become leaders in their field. PIs, mid-level and early career researchers of all groups will be invited to present their work at consortium partners' institutes to stimulate intellectual interaction and explore new areas for joint research. The HHH applicants will act as mentors for the early- and mid-career scientists and we will launch a Young Investigators Grant. In addition, prof. Jolien Roos (director DCVA) has committed to contribute as mentor and coach for the talents. During the project, two congresses will be organized by and with the young and mid-level researchers enabling them to show(case) their work.

All young and mid-level researchers in the project can qualify for the DCVA (HHH co-funder) Leadership Program. This program creates a network of talented and dedicated people who are seen as leaders in the future cardiovascular arena. The program is being directed by Professor Leon de Windt, Chair of the DCVA Talent Program. Every two years a group of 15 participants will start the 2-year program. These participants are divided in multidisciplinary groups having roots in various segments of the cardiovascular field. Each group works on a complex current challenge provided by partners of the DCVA. Besides 3 training days, participants will go on a trip, in Holland and possibly abroad, to work collaboratively as a group on their challenges. In addition, the young and mid-level researchers will also take courses on the topic of intellectual property management, project management, lab leadership etc. to develop their leadership skills.

4.2 Project management

The HHH consortium consists of 23 members including 14 co-applicants, 6 co-funders and 3 co-operation partners. A project with this scope and of this scale requires robust project management organization.

Project management organization HHH: A project management organization will be established to safeguard the progress of the project, and coherence between the WPs within the project. A transparent organizational structure has been developed with clearly defined roles, responsibilities, and governance procedures. This will allow efficient coordination of the work between the consortium members, mitigation of risks, and efficient and effective response to any emerging issues in the development of the project. The project management organization of HHH will consist of three main bodies: the Advisory Board, Project Management Team and Governance Board (Fig. 4.2.1).

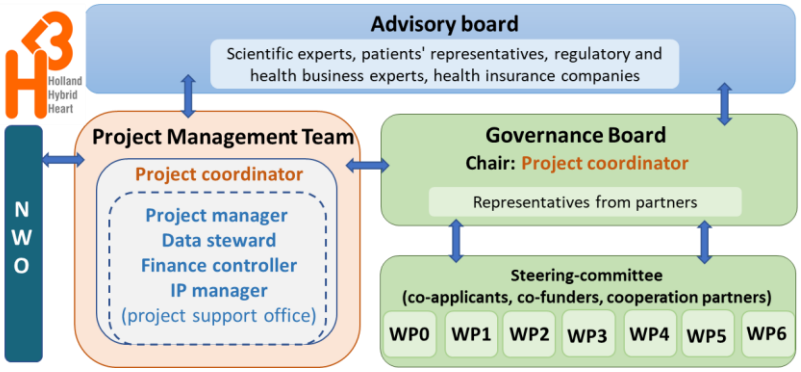

Figure 4.2.1 : *Project management organization HHH*

The Advisory Board will incorporate all stakeholders. It will consist of up to 6 international key opinion leaders with acknowledged reputations in the field of soft robotics, TE, ethics and medicine. Importantly, patients/patient representatives and patient organizations have a seat on the Advisory Board. Furthermore, regulatory experts and health insurance companies will complete the Advisory Board. The board will act as an independent body to evaluate progress during plenary project meetings and provide input on the project activities, including ethical and other considerations from a patient's -including their relatives- perspective. The input from the Advisory Board will be critical in guiding the project activities.

The Governance Board will be the highest authority of the consortium, and will consist of one representative from each of the partner groups i.e. one representative per WP (co-applicants) , co-funders, cooperation partners and will be chaired by the **project coordinator**, Prof. Jolanda Kluin. The Governance Board will set strategic direction and monitor completion of critical objectives, approve continuation of project phases and release of funding. The **Steering-committee** will be involved in coordinating collaboration between all partners of the consortium for the tasks defined within the work-packages (WP0-6). The Steering-committee will report the results and status of WP progress to the Governance Board on a regular basis. WP teams, under the supervision of a WP leader will be responsible for efficient and effective implementation of the work associated with a specific WP. WP leaders are responsible for monitoring the progress of the activities towards the specific deliverables and milestones. Open and intense communication has our highest priority and will be monitored accordingly by the project coordinator. A confidential digital platform will enable streamlining the exchange of knowledge, results and feedback between partners. Frequent project meetings will take place for updates on the work progress.

The project Management Team will be headed by the project coordinator, Prof. Jolanda Kluin who will have the responsibility for the management and governance of the project adhering to relevant NWO regulations and the Funding & Collaboration Contract. Prof. Kluin has obtained the required expertise to lead large public private partnerships, for instance as coordinator of the H2020 FET programme. Prof. Kluin will be supported by a dedicated project support office, including a **Project Manager**, **Data Steward** (management of data handling and storing), **Finance Controller** (financial coordination) and an **IP Manager** (all from EMC). The Project Manager will support the programme coordinator and lead administrative and organizational tasks (0,5 FTE). The Project Manager will be the point of contact for NWO liaison, for current and potential future partners, and will take the lead in day-to-day project management activities and communication with partners and external communication. The Financial Manager (0,1 FTE) will lead the financial management, oversees the programme budget, allocates money and does payments to the partners, delivers requested financial reports, and receives requests for budget shifts. The IP Manager (in-kind contribution from EMC) will coordinate knowledge management, innovation management, dissemination and communication guidelines and is involved in monitoring and managing exploitable results.

5 Productive interactions

5.1 Stakeholder engagement

Organization of stakeholder engagement: Stakeholder engagement will be coordinated by the Project Management Team. The Governance Board along with the project coordinator will be responsible for developing the stakeholder engagement strategy and overseeing stakeholder engagement, while the project manager will be responsible for coordinating the day-to-day activities.

Special module for user engagement: Because user engagement is the core in the development of HHH, engaging all users and stakeholders is the central activity in WP0. The **'UserEngagement and DesignThinking Lab'** of the Industrial Design Lectorates at Saxion University of Applied Sciences offers all possibilities to consult that user at an early stage. The combined lab offers opportunities for conducting all kinds of user research, such as focus groups, interviews or one-to-one user research. The lab offers materials and tools for teams to explore and build first prototypes of products that emerged from previous 'design thinking' sessions. The lab is equipped with two cameras and a microphone. The recorded material can later be reviewed in detail to find out what was actually said, and what actually happened.

A detailed engagement plan will be developed at the project start and will be updated annually (WP6). An initial plan for the stakeholder engagement is given in the table below.

Stakeholder	Objective of the stakeholder engagement strategy & purpose of various activities	Type of activities and their timing
HF patients	• Investigate acceptability of HHH concept for the treatment of heart failure • Provide awareness on the impact of HHH as compared to MCSDs or donor heart transplant as treatment strategies • Retrieve user aspects that need to be included in the design of the HHHH	Throughout the duration of the project • Members of stakeholder panel in 'UserEngagement&DesignThinking Lab' activities • Member of Advisory Board • Questionnaires, interviews, focus groups • Patient information brochure • Website and social media
Patient organizations	• Co-develop a communication strategy towards patients, caregivers and general public, as well as assist in implementing it • Involvement in dissemination of project outputs / outcomes	Throughout the duration of the project • Member of Advisory Board • Workshops & Conferences • Members of stakeholder panel in 'UserEngagement&DesignThinking Lab' activities

Researchers	• To disseminate scientific knowledge generated in the project	Throughout the duration of the project • Research articles • Conferences /workshops • Scientific Collaborations
General public/ (Dutch) Society	• Investigate acceptability of HHH (a soft robotic total "artificial" heart) for the treatment of HF patients • Provide awareness on the impact of HHH as compared to MCSDs or donor heart transplant as treatment strategies	Throughout the duration of the project • Societal dialogue, panels, questionnaires, via social media, press releases, website and workshops
Healthcare professionals	• Investigate acceptability of, and preference for, the HHH for the treatment of HF patients • Retrieve aspects that still need to be developed for implementation of HHH in clinical care • HHH to be taken up in clinical guidelines	Throughout the duration of the project • Through medical and professional associations • Scientific papers • White paper • Seminars / workshops
Scientific & technical community	• To ensure knowledge transfer through dissemination of research results. • For a wider impact of the research results – to use the technology and scientific insights for other applications	Throughout the duration of the project • Peer-reviewed papers in scientific journals • Presentations at (inter)national conferences, workshops
Healthcare payers	• To ensure reimbursement of HHH-based treatment	Throughout the duration of the project • Early HTA to confirm cost-effectiveness of HHH • Member of Advisory Board • Members of stakeholder panel in 'UserEngagement&DesignThinking Lab' activities
Industry	• Define the manufacturing requirements to ensure successful commercial production	Towards the end of the project • Trade events • MedTech conferences • Partnership negotiations
NWO	• Liaising to ensure smooth operation of the project	Throughout the duration of the project • Progress reports and financial reports

5.2 Communication

The HHH communication strategy will meet the following objectives:

- To provide all stakeholders with relevant and accurate information related to the project in a timely manner. The communication will be tailored to the specific needs of the recipients.
- To obtain relevant and accurate information for the project from all stakeholders, to maximize project outcomes and impact.

Organization of communication: The Project Management Team will be responsible for coordinating the communication activities. The project manager will be responsible for coordinating the day-to-day communication activities and the project leader will be responsible for oversight of project communication.

- **Involvement of science journalist:** To communicate the scientific and technological knowledge generated within the HHH project to the general public and beyond the scientific community, we have involved a science journalist, Suzanne Streefland who is experienced freelance journalist for national radio and television in the Netherlands, as a cooperation partner in the consortium. She is actively involved in broadcasting every week on live television about news and science for Atlas (NPO). She will be involved

in writing a communication plan and designing and maintaining contacts with the press, and frequent posting on social media. For all these activities including the cameramen and equipment, travel, we have reserved €120K for this in the HHH budget.

- **Other communication activities:** A detailed communication plan will be developed at the project start and will be updated annually (WP6). Broadly, our communication activities will be divided into internal communication activities (to ensure accurate and timely information and data sharing between project partners) and external communication activities (with external stakeholders). An initial plan for the communication activities is given in the table below.

Purpose	Means and type of activities	Timing
HHH consortium (internal communication)		
Accurate and timely sharing of data and information between project partners.	WP meetings; consortium meetings; Internal symposia/webinars to accommodate junior researchers (PhDs, Postdocs) - the format and timing will be aligned with their needs.	Monthly for WP meetings; Annual for consortium meetings; Internal symposia/webinars will be organized at regular intervals. Besides the scheduled activities above, in reaction to unexpected or important developments, the project partner will share information with the consortium.
Communication with Patients		
To raise awareness on, and to counsel the patients on the clinical treatment options, including HHH. **To gain understanding of their perspective regarding HHH-based treatment.**	Meet patients at the hospital – inform them through sharing documents for clinical study; counselling consult by healthcare professionals.	Regular communication to collect as well as incorporate feedback. Furthermore, in reaction to patients' feedback on the HHH, we will encourage dialogue to identify and address worries and attention points. Their feedback will be an important aspect of product design & fabrication.
Communication with patient organizations		
To partner during the project for involvement in the dissemination strategy of project outcomes.	Meetings, conferences & workshops, social media, website.	Regular meetings (2 times a year) and other communication will be done on regular basis.
Communication with general public		
To raise awareness and understanding of the applicability of the HHH in clinical practice.	Science journalist Suzanne Streefland and communication office of Erasmus will communicate the results of HHH project through website, social media, infographics and videos. The information will be channelled through popular science institutes, newspapers and participation in public events.	Regular communication activities will be planned. Moreover, communication will be undertaken in reaction to developments in society and science.
Communication with healthcare professionals		
To understand their perception of the clinical usability of the HHH, and its benefits. **To encourage healthcare professionals involved in cardiac care to implement the HHH.** **To ensure uptake of project results in clinical guidelines.**	Involvement in scientific and professional associations, (inter)national seminars and consortium-initiated, newsletters, scientific papers, training materials, workshops.	Regular communication activities will be planned, especially around national and international scientific meetings of the various medical societies and scientific publications.

Communication with scientific community		
To encourage uptake of scientific information resulting from our project, and to further identify and investigate related pertinent research questions.	Peer-reviewed, open access scientific papers, seminars (inter)national and consortium-initiated, workshops.	Regular communication planned at project milestones and publication of scientific papers. In addition, communication will be undertaken in reaction to important scientific and technological developments in the field.
Communication with industry		
To obtain prototype and production requirements to ensure successful exploitation. To inform the industry on feasible commercially viable outputs resulting from the project. To explore potential partnerships.	MedTech conferences and trade events, existing contacts, networking meetings, website and social media.	Regular communication activities will be planned. In addition, communication will be undertaken in reaction to industrial or business developments, both within the project and within the field.

5.3 Monitoring & Evaluation

a) **Strategy** of Monitoring and Evaluation: to monitor the progress of the project, report on the deliverables and evaluate progress and future strategy (including evaluating go/no go moments) during consortium meetings we incorporate the following strategies:

- Monitoring strategy - The project activities will be monitored at the regular consortium meetings. The main goal of the monitoring will be to collect data about the progress of the project using key performance indicators as defined in the impact pathway indicators in table 1B Annex.
- Evaluation strategy - The key performance indicators (KPIs)/deliverables that are closely tied to the project goals will be defined in each WP. This will enable a reflective approach. The project will be evaluated by comparing these pre-defined KPIs against actual progress, to assess if the project is going as planned or if any adjustments to tasks are needed to deliver the intended impact. The evaluation results will be reported to all stakeholders annually.

b) **Organization** of Monitoring and Evaluation**:** The Governance Board will oversee the overall monitoring and evaluation of the HHH project. The project leader will be responsible for the monitoring and evaluation activities with the support of the project manager. The WP leaders will be responsible for monitoring progress at each WP meeting and reporting the progress to the project leader and the Governance Board.

c) **Activities** of Monitoring and Evaluation**:**

- Defining KPIs/deliverables: The purpose of this is to define a set of deliverables/indicators which we aim to achieve throughout the project. We will set the baseline value (where applicable) and define the target value we aim to achieve. We have already pre-defined such deliverables as output indicators in table Annex 1B and will refine them at the start of the project.
- Performance measurement: The purpose of this is to compare the expected performance of the WPs with the actual performance. The performance of each WP will be monitored at regular WP meetings (every month) and evaluated and discussed at the consortium meetings (annual).
- Evaluation: The purpose of evaluation is to analyze the monitoring data that are collected at the consortium meetings. Evaluation will be conducted annually. The information during the evaluation process will be used to identify gaps in implementation and adjust the implementation in the following year to ensure the intended impacts are delivered.

5.4 Capacity strengthening

The objective of our capacity strengthening strategy is to improve the human resources and intellectual property of the various partners in the consortium as well as other external stakeholders to enhance the potential for successful execution of project outcomes. Our structured approach during the HHH project will provide a wide variety of stakeholders with the opportunity to strengthen their capacity:

- **Technical skills and scientific expertise of young researchers:** The PhDs and PostDocs involved in the project, gain significant experience and expertise through participation in the project. Formally, their professional and personal development will be the responsibility of their PI and will be overseen by the respective HR departments of their affiliated universities/medical centres. The multidisciplinary nature of the consortium ensures that the knowledge of all researchers is strengthened through the understanding of, and involvement in, each other's work.
- **IP capacity of consortium**: The knowledge generated within the HHH project will be used to apply for patents and hence strengthen the IP capacity of partner organizations. All IP will be licensed by the spin-off company NewCo.
- **Knowledge sharing with the scientific community:** Scientists will be energized with new scientific insights and technical know-how in the fields of heart failure, tissue engineering and soft robotics, that could lead to new streams of research.
- **Empowerment of health professionals and patients**: Patients with heart failure will be empowered with a novel and personalized intervention strategy to increase their survival chances and provide a better quality of life. Health professionals caring for these patients will be able to provide them with accurate recommendations on how to treat HF.
- **Empowering patient organizations**: Patient organisations will receive new tools and strategies to empower their members and affiliated entities to better address HF treatment.

6 Scientific objectives & research questions

6.1 Scientific objectives

Soft robotics has not previously been used for functioning artificial organ development, and soft robotics and *in situ* TE have never been combined before. As such, the HHH project has potential high risk but also high gain. With the complementary consortium partners that are world leading in their respective fields of expertise, we expect to achieve Proof-of-Principle for full functionality and biocompatibility of this breakthrough development in a large animal (sheep) model within the lifetime of this 7-year project. The consortium has defined the following SMART objectives towards HHH Proof-of-Principle:

Specific	Measurable	Achievable	Relevant	Timely
Develop soft robotic heart matrix and actuators	Prototype available	EMC & AMOLF previously developed bioinspired soft robots	To provide a soft cardiac total artificial heart	Month 60
Optimize *in situ* TE	Inner lining of endocardium and heart valves available	TU/e & EMC previously developed TE heart valves	To ensure artificial heart hemo- and biocompatibility	Month 60
Include passive regulation and monitoring	Prototype available	AMOLF, UT & Saxion previously developed an autonomously operated fire robot	To enable autoregulation to reduce impact on body, and monitor functioning of device during operation	Month 60
Integrate TE and soft robotics materials	Prototype functional in *in vitro* simulation	Expertise on materials and 3D weaving at Saxion, EE Labels & UT	To optimize design and durability for use in patients	Month 72

Provide proof of concept in relevant *in vivo* model	Proof-of-principle study finalized	EMC & TU/e previously validated TE valves *in vivo*	To support ongoing development and dissemination	Month 84

6.2 Scientific relevance

Although no complete artificial organ based on **soft robotics** has been developed yet, development of *ex vivo* and *in vivo* assist devices has demonstrated the attractiveness of soft robotics for this purpose. Based on the ability to change shape in response to contact with any surface, soft robot grippers have been suggested as part of improved prosthetic hands[24]. Additionally, several previously developed advanced soft robots provide a basis for the development of a soft robotics-based heart[1,2,25,26]. A soft direct cardiac compression device, which can be placed around a failing heart to support the heart's pump function has been shown to function well in an *ex vivo* Proof-of-Principle study[13,27]. In another study, poro-elastic foam was used to manufacture a basic cardiac pump, which could pump fluids in a benchtop setting[28]. The feasibility of seeding a soft robotics matrix with (rat) heart cells was shown in a swimming robot that mimicked a ray fish[29]. In this robot however, the force propelling the robot came from cells responding to an external electrical field. In the current project, the first fully functional soft robotic heart will be developed, in which the soft robotic components will provide the force needed for natural cardiac motion.

In addition to soft robotic technology, the consortium will use ***in situ* TE** to ensure biocompatibility of the HHH. *In situ* regeneration is based on a cell-free bio-resorbable synthetic scaffold implant, to which endogenous cells adhere. This transforms the scaffold into living tissue after implantation, as the scaffold is gradually replaced by endogenous cells and a cell-produced extracellular matrix, absent of pathological calcification, and in pace with cell-driven scaffold resorption. Apart from heart valves, *in situ* TE has so far been investigated for applications such as vascular grafts, nerve and bone regeneration[30]. The *in situ* TE technology previously developed by HHH consortium partners to generate pulmonary valves[31] will be adapted to generate a living biocompatible lining of the endocardial space and (artificial) valves. For this, synthetic materials will be used that offer high control of scaffold design and manufacturing, which allow fine-tuning of desired mechanical properties and resorption rate, and potential incorporation of bioactives to guide neotissue formation. This will generate new scaffolds that are biomechanically more advanced and can withstand harsher haemodynamic conditions. The cell-free and synthetic scaffold basis will endow the HHH with off-the-shelf availability at substantially reduced costs and logistic complexity compared to other TE approaches.

Apart from greatly advancing the state-of-the-art of the basic technologies building the HHH, combining soft robotics and *in situ* TE to attain Proof-of-Principle for an *in vivo* functional artificial soft actuated heart requires cutting-edge knowledge of how to integrate all components, such as the soft robotics elastomeric shell and actuators with the TE scaffolds. Combining soft robotics and TE in this project will render a new technology in itself, with many future applications inside and outside medicine.

6.3 Scientific impact

The HHH fuses deep understanding of the physiology of the natural heart with profound new developments in the fields of soft robotics, designer materials, regenerative medicine, and material science:

Scientific Breakthrough 1: **Soft robotic total artificial heart.** Use of soft and flexible materials to truly resemble the contracting and mechanical behaviour of the human heart. The consortium will select a non-stretchable, yet easily bendable, durable material, such as woven durable fibers (e.g., thermoplastic polyurethanes or Dyneema fibers) and embed designed actuators to truly resemble the physico-mechanical motion and contraction of the human heart.

Scientific Breakthrough 2: ***In situ* tissue engineered inner lining**. Integration of *in situ* TE inner lining to form a layer of the patient's own living cells. Together, natural motion and living cells will avoid adverse haematological (thrombosis and bleeding) and immunological (rejection) reactions and minimize biocompatibility issues. This will be achieved by generation of polymer scaffolds (e.g. via electrospinning)

and/or coatings that will be tested regarding biocompatibility (including immune responses and blood compatibility) and neo-tissue formation under the hemodynamic conditions occurring inside the HHH.

Scientific Breakthrough 3: **Development of passive fluidic control and embodied intelligence.** This enables safe and efficient driving of the HHH and as such creates the possibility of driving without a driveline but with transcutaneous energy delivery. Embodied intelligence and feedback (e.g., conductive fibers) enables compliance and autoregulation that is far beyond the possibilities of today's devices.

Scientific Breakthrough 4: **Integration of all components and manufacture of the HHH.** This enables translation to the clinic and other applications. Using non-stretchable and durable soft materials, new 3D weaving techniques, HHH can bridges the development pipeline from basic understanding and design to full pre-clinical testing, to get ready for clinical translation.

Breakthrough 1: Soft robotic total artificial heart	
Research fields of interest	Scientists, companies developing soft robotic devices in- and outside the medical field.
Why these fields are interested	Knowledge created regarding soft robotics especially towards material selection and manufacturing can be used to develop other robotic devices.
Existing relevant contacts and how they are used	Collaborations with our huge network of a wide range of scientist and press articles by science journalist Susanne Streefland will accelerate the dissemination next to scientific publications and conference talks.
Breakthrough 2: *In situ* tissue engineered inner lining	
Research fields of interest and new methods	Scientist, physicians, medical companies working on devices and surgical instruments that come in contact with blood.
Why these fields are interested	Our *in situ* TE inner lining will enable multiple applications such as implants with blood-material interfaces, like stents, vascular grafts or existing cardiac assist devices. They may also find application in the blood-contacting parts of extra corporal medical devices like dialysis machines, extracorporeal membrane oxygenation (ECMO), heart-lung machines, or more innovative applications, like bioartificial kidneys.
Existing relevant contacts and how they are used	Consortium members from TU/e and Erasmus MC are world-renowned experts in TE and medicine and have a great network. Next to scientific publications and conference talks, press articles by science journalist Susanne Streefland will accelerate the dissemination.
Breakthrough 3: Development of passive fluidic control and embodied intelligence	
Research fields of interest and new methods	Scientists, companies developing soft robotic devices in- and outside the medical field.
Why these fields are interested	In fields where rigid electronics cannot easily be incorporated, fluidic circuits provide an alternative analog control strategy to embody simple algorithms.
Existing relevant contacts and how they are used	The co-applicants AMOLF and Saxion are well known experts for fluidic circuits and will disseminate the project results to achieve the biggest impact.
Breakthrough 4: Integration of all components and manufacture of the HHH	
Research fields of interest and new methods	Scientist, physicians, medical companies working on organ replacement and wearable robots (e.g. limb) as well as companies outside the medical field.
Why these fields are interested	The soft robotic technology can be used to develop other off the shelf organs as well as improved limb replacements.
Existing relevant contacts and how they are used	Collaborations with a wide range of scientist and press articles by science journalist Susanne Streefland will accelerate the dissemination.

Plausibility to achieve the targeted breakthrough

The HHH is a radical new and highly disruptive concept based on a combination and extension of the aforementioned technologies. Since 2018, members of our consortium (EMC, AMOLF, TU/e, Evos) have explored the potential of developing a bioinspired soft robotic heart. Supported by a Horizon 2020 FET Open programme, the project team has laid the groundwork of specification and development of the hybrid heart components and the first functional prototypes. Based on our initial results, we have identified the challenges and next steps of the process towards delivering the first HHH. The FET Open team has established to date 3 prototype soft robotic hearts, that we have identified the most suitable (Fig. 6.3.1). Each prototype has its own shape, materials, and behaviour. The first prototype consists of a silicone elastomeric matrix, embedded with McKibben actuators (a)[32]. When the soft actuators are pressurised, they contract longitudinally, ejecting 'blood' from the internal chamber. The second prototype consists of so-called pouch motors that are constructed from heat-sealed polyurethane sheets (b)[33]. These soft actuators contract laterally when pressurised, and similarly, eject 'blood' from the internal chamber. Differently, the third prototype has a central soft fluidic actuator that, when inflated, contracts two chambers that are connected by wires (c). Patents of all three prototypes have been filed and will be hold by the spin off company NewCo.

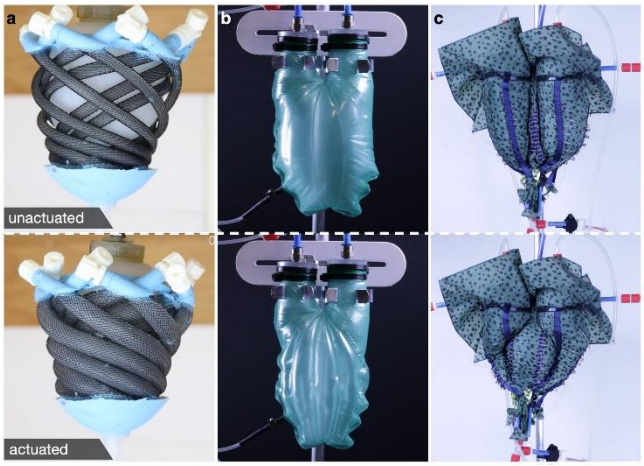

***Figure 6.3.1**. Current Development Process*

7 Project overview

7.1 Project structure and coherence (Annex 2)

Research methodology

The HHH project is divided into six work packages (WPs). The requirements for the HHH will be determined in WP0 and continuously reassessed throughout the development of the HHH (Fig. 7.1.1).

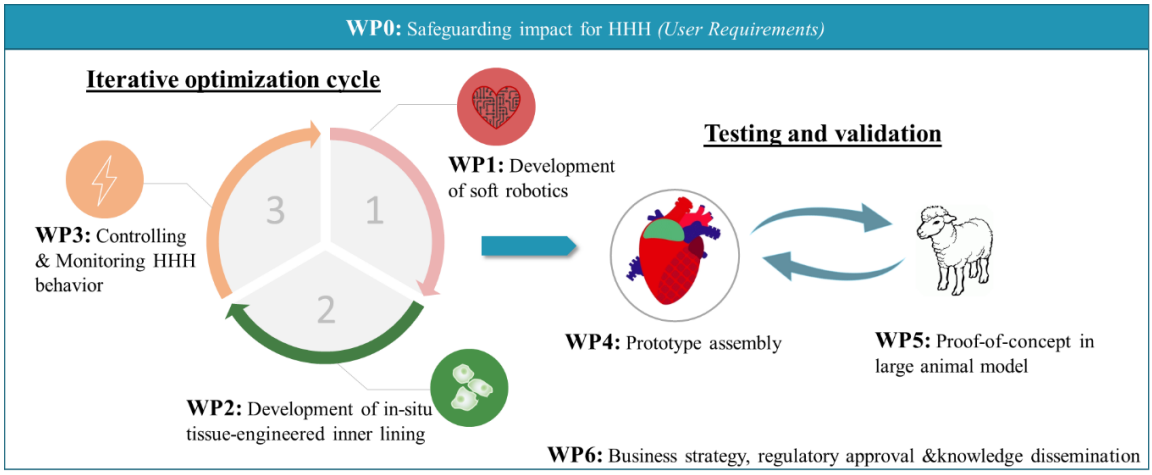

***Figure 7.1.1.** HHH development cycle*

The separate components of the heart will be developed in parallel in WPs 1-3, and integrated in WP4, after which *in vivo* validation and Proof-of-Principle studies will be performed in WP5. This methodology will provide the consortium with a flexible and effective way to develop the HHH, while open communication between the partners will ensure that opportunities for alternative research and development directions will be immediately explored when relevant.

In **WP0** we will ensure impact of the HHH by performing an extensive stakeholder analysis, an interface analysis, analysis of translation from user-to-system requirements and the design of the architecture of the entire system. Special attention to the ethical considerations is given throughout the entire project and the societal impact is determined. Finally, no HTA models and data related to implementation of the HHH are available yet. Therefore, we will construct a conceptual model for eHTA of the HHH in comparison with current alternatives (i.e. intravenous drug support, MCSD, and donor heart). Briefly, a conceptual model based on a systematic review of available HTA models related to heart transplantation and ventricular assist device implantation will be built, and systematic reviews of characteristics and outcomes of these procedures in different patient groups performed. Building on this, and using a Delphi process including different stakeholders in the healthcare sector (healthcare institutions, patients, clinicians, healthcare payers), the eHTA is constructed.

In **WP1** the active soft robotics components of the HHH will be developed and integrated to reliably mimic cardiac movements. The arrangement and design of these actuators defines the range of motions the HHH can perform. The pumping volume of the HHH can be optimized by, e.g., varying matrix design and material. The shape of the heart will be designed and tested, both in computational models[27] to determine the optimal behaviour as well as in prototypes to test contraction patterns and pump function *in vitro*. For the latter we will use mock loop simulation set-ups that mimic the clinical situation. Essential in selecting the materials is the durability of the HHH; we therefore aim for non-stretchable durable materials like woven durable fibers, proven to be durable in clinical use (e.g., aortic grafts). During development of these (novel) materials, compatibility between the elastomeric matrix and the TE scaffold will be optimized.

In **WP2** the materials and fabrication methods for the HHH *in situ* TE inner lining will be developed and assessed. This includes the generation of polymer scaffolds (e.g. via electrospinning) and/or coatings that will be tested regarding biocompatibility (including immune responses and blood compatibility) and neo-tissue formation under the hemodynamic conditions occurring inside the HHH; and the in integration of scaffolds with the soft robotic matrix.

In **WP3** the focus lies on controlling and monitoring the beating of the HHH. Fluidic circuits will be used to transform a continuous inflow from a hydraulic pump into pulsating output that will activate the soft robotic muscles in the heart. The circuits will be designed to passively adapt to variations in the physiological conditions. Additionally, soft sensing fibers will be incorporated within the elastomeric matrix, to detect motion and provide feedback to optimize motile behaviour. The sensor data from the HHH will be transmitted from inside the body and analyzed in the cloud in order to provide owners with insight on the behaviour of the heart.

In **WP4** design and fabrication of all HHH components will be performed, with the focus on fully integrating all components in a single device. All components of the soft robotic heart and the TE scaffolds will be integrated and bio- and haemocompatibility will be validated. In this WP the partners will test the functionality and durability of the HHH *in vitro*, using an advanced isolated, pulsatile mock loop platform. This offers full control of all cardiac parameters and the possibility for inspection of the HHH with visual endoscopy, ultrasound, CT and MRI. During this test phase the data from the heart will be used to calibrate the insight platform and that data will also be used to inspect the HHH itself.

In **WP5** final Proof-of-Principle will be achieved by implanting the HHH both in an acute as well as chronic sheep model. The chronic experiments will take place in the high-end animal facility at Medanex.

In **WP6** we will develop a business strategy and establish a private company called ‘NewCo’ that will hold all the relevant IP rights, secure additional financing and lead commercial negotiations. Further, regulatory approvals needed for first-in-man studies and beyond will be prepared. Finally, WP6 will provide a framework for IP and legal management and in addition, encompasses communication and dissemination activities.

Beyond the proposed project

Following this 7-year project, in 2030 we will start GLP-animal studies and aim to perform the first-in-man HHH implantation as compassionate use halfway the next decade (Fig. 7.1.2).

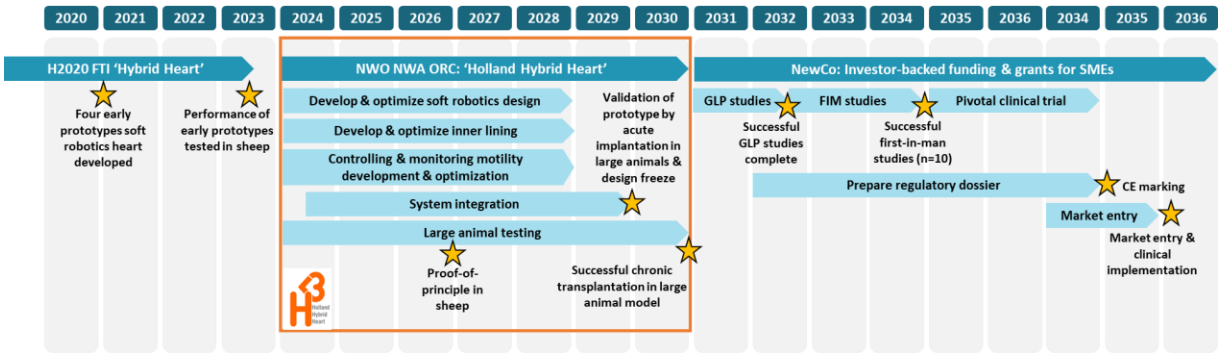

Figure 7.1.2 *Timeline towards clinical implementation*

7.2 Description of the work packages

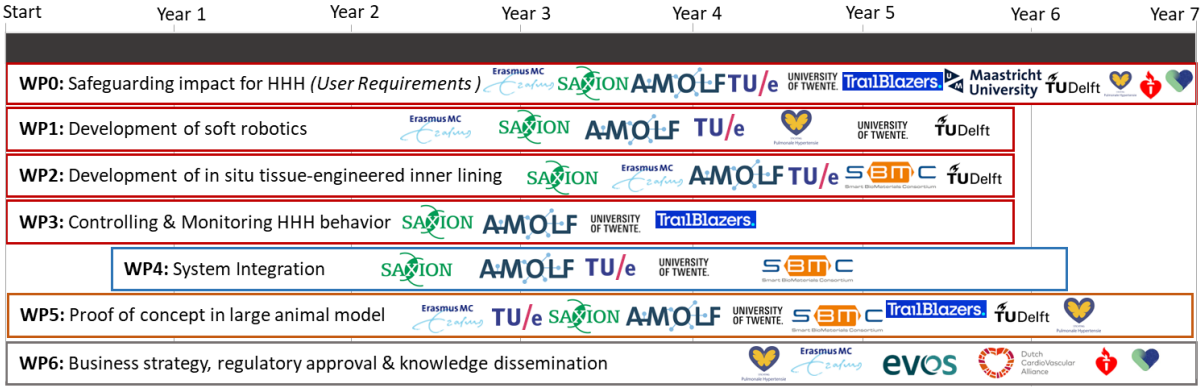

Figure 7.2.1. *Timeline of the HHH WPs*

Work package number	0
Work package title	Safeguarding impact for HHH
Work package leader	Saxion (Research group Industrial Design)
Involved partners	All partners
Start date	M1
End date	M84

Since HHH is a revolutionary development, it is important to carefully design not only the technology itself but also anticipate on future use and societal impact of the HHH. This is a design challenge that requires continuous interaction between technology development and user acceptance. WP0 addresses this challenge.
The first objective of WP0 is to design an overall system architecture for the HHH, integrating and connecting various components. As the system design takes shape, user requirements regarding the use will be gathered from primary stakeholders, such as patients, physicians, therapists and care givers. These user requirements are translated into system requirements and are integrated with the overall system architecture.
The second objective of WP0 is to anticipate the future use and acceptance of the HHH by patients and its impact on society in general. A wide range of stakeholders is actively involved in co-design sessions to discuss not only the anticipated practical use of the HHH, but also to discuss the acceptance and impact of such technologies.

Objectives

- Design overall system architecture for the HHH;
  - Map out dependencies and interfaces between system components;
  - Define list of user requirements.
    - Reveal the demands and wishes of the stakeholders (physicians, therapists, care givers and a special focus to patients).

- Translate user requirements into system requirements
- Anticipate future use, acceptance and impact of the HHH;
  - Identify driving factors for acceptance and quality of life;
  - Evaluate direct and indirect consequences of this technology;
  - Evaluate the societal impact throughout the project.
  - To facilitate using insights into ethical and societal impact in day-to-day research and development
  - Perform early Health Technology Assessment (eHTA) with cost-effective model.

Methodology

The two objectives are closely related and therefore executed in parallel.

- A system engineering approach is used for the design of the overall system architecture. In particular the *FunKey methodology* will be applied. System engineering aims to structure the design and development of complex, multidisciplinary systems such as the HHH. It prescribes approaches for various product development phases ranging from preliminary design and conceptual design and detailed design. The FunKey architecting methodology will be used to design the overall system architecture. Development of the HHH requires specialist developers and researchers. The specialists have a view of their own task and discipline with limited or lacking overall context information. Funkey Architecting enables system developers to map out in a structured way the key drivers that define the system's complexity and identify interfaces between the separate system's components to ensure that the individual components deliver to the overall aims of the system.
- A *scenario based design methodology* is used for the design and anticipation of future use and impact of the HHH. Scenario based design is a methodology that supports designers and design teams by providing an explicit means to explore future use. For the HHH development, an important benefit of this methodology is that it allows for important stakeholders to be actively involved in the design and development process, even before a detailed design is available; in early stages of development, mock-ups or interactive visualizations can be discussed with stakeholders and lead to additional user/product requirements.
  Scenario based design also supports the communication that takes place with the various stakeholders regarding the evaluation of product use. Throughout the development process, scenarios can be used to capture different perspective of the product, including technical, user and societal perspectives. Combined, scenarios can form a roadmap to guide product development.
  The Ethical Parallel Track (EPT) is a methodology that includes a set of different interventions, aimed at the identification and inclusion of the Ethical, Legal, and Social Aspects (ELSA) in a process of technology development and implementation. Ensuring early detection and inclusion of possible ethical issues facilitates a more smooth implementation of the final technology.

The EPT includes a broad range of stakeholders, including project partners and researchers, patient organizations, and clinicians. Researchers from WP0 will be co-executors of the EPT, in order to optimally include all relevant input generated in the HHH project.
An analysis of (un)intended positive and negative social consequences.
An eHTA will be used to document the results of the scenario based design activities. For the eHTA, systematic reviews will be performed according to PRISMA guidelines. Outcome data of left ventricular assist devices and total artificial heart transplant will be derived from the EUROMACS database of the European Association of Cardio-Thoracic Surgery (EACTS) to determine outcomes and determinants of outcome in current standard care (SC). EUROMACS is the largest European database concerning outcomes of device therapy for advanced heart failure. A microsimulation model will be developed using the data derived from the systematic reviews and EUROMACS database. Microsimulation methodology allows for translation of population-based patient outcome estimates to patient age and sex specific outcome estimates. These patient specific outcome estimates can include clinical outcomes, but also can be combined with quality of life and cost estimates (resulting

from the scenario based design sessions) allowing for patient age and sex specific (e)HTA. The conceptual framework will be developed by a multi-stakeholder group.

Description of research activities

For objective 1

- **T0.1: Interface analysis (Saxion) (M1-M24).** The analysis of the interfaces of the separate components in relation to each other based on the Funkey Architecting methodology, to reveal key drivers for system components' dependencies[34].
- **T.0.2: Translation of user requirements and system interfaces to system requirements (Saxion MT&ID, AMOLF, E MC, TU/e, UT, Trailblazer) (M12-M24).** Translation of system requirements to component system requirements and architecture.

Key performance indicator: Overall system architecture, defining system and sub systems, components and underlying interfaces.

For objective 2

- **Task 0.3 Ethical Parallel Track (All) (M1-M84)**
  - **Task 0.3.1 (M1-M6): Organization of the Ethical Parallel Track**. Prepare the EPT in collaboration with other researchers involved, development and redesign of interventions that we aim to apply in HHH. Interventions include i.e.: ELS Readiness Checks; Impact Anticipation; Stakeholder dialogue/representation; Impact assessment and evaluation; Feedback for redesign professionalization.
    Task 0.3.2 (M5-M72): Execution of the EPT. We execute the EPT. The main structure will include (a) a start-up meeting with all project partners to identify research motivations, dilemma's, and priorities; (b) workshops and interventions with researchers, project partners, and external stakeholders; (c) input sessions with all researchers from WP0 to gather their inputs and analyse the ethical and societal implications of their findings;(d) bi-yearly sessions with all consortium partners to feed back the findings regarding ethical issues and align priorities.
  - **Task 0.3.3 (M40-M72): Redesign and communication.** Incorporating the design and execution of the HHH EPT and the project results in the methodology of an EPT for innovations in healthcare, including reporting in scholarly publications.
- **T0.4: Scenario-based Design (Saxion, EMC) (M1-M48):**
  - **0.4.1 Stakeholder Analysis.** In preparation to stakeholder involvement (as part of the scenario based design methodology) an extensive stakeholder analysis is conducted. This analysis identifies which people and how they are related to the HHH.
  - **0.4.2 Co-design Sessions.** Depending on their relation to the HHH (e.g. primary or secondary users, positive or negative attitude) an appropriate method for active involvement in the design process can be selected. Throughout the HHH development process, co-design sessions involving various stakeholders (following from T2.1) will be conducted to gather, evaluate and refine use cases, user requirements and future use situations of the HHH.
- **T0.5 Early health technology assessment (Erasmus MC) (M1-M48):** An eHTA study will be included to provide: 1) the evidence-base for defining of the target patient population(s) in the trial in a multi-stakeholder working group (including clinicians, patient representatives, ethicists and health economists/payer representatives); and 2) the instruments to define clinical outcomes, quality of life and health care costs in the first-in-human trial. A cost-effectiveness model for HTA of the Hybrid Heart versus the current heart failure treatment options will be developed, which enables to investigate how sensitive the cost-effectiveness is to changes in its characteristics and to estimate the maximum costs in order to be cost-effective. We will explore the reimbursement landscape and barriers to the uptake by payers and policy makers. *Key performance indicator*: e(HTA) model.

Productive interactions (co-design and co-creation)

Saxion ID&SFT with all partners: compile user requirements. Saxion ID&Ethics with all partners: Ethical parallel track. Saxion ID&MT&SFT: Interface analysis. Saxion ID&MT&SFT: Translation user requirements and system interfaces to system requirements and architecture. Saxion ID&SFT: Patients' and technology acceptance.

Contribution to project (impact)

WP0 contributes to the project by:
1) providing an overall system architecture for the HHH that can be used to guide product development throughout the project and

2) providing a product roadmap that describes the HHH in various stages of development from a technical, a user and a societal perspective. The roadmap is constructed during the research, in close collaboration with various stakeholders. This contributes to the acceptance of the HHH and allows the development of the HHH to take user and societal requirements into account from the start.
3) developing an eHTA that will guide the development of the HHH. Subsequently, costs will be added to the model to enable cost-effectiveness evaluation, from a payer's and a societal perspective. These models enable us to investigate how sensitive the cost-effectiveness of the HHH is to changes in the characteristics (e.g. durability, infection risk) and performance. These models also allow us to estimate what the maximum costs of the HHH can be in order to be cost-effective, given the current threshold level of costs per quality adjusted life year (QALY). This is an essential step allowing to demonstrate the potential gains of the HHH in terms of costs and health benefits in different scenarios towards payers and health policy makers.

Work package number	1
Work package title	Development of soft robotics components
Work package leader	Ali Sadeghi-Jolanda Kluin
Involved partners	UT, EMC, TU Delft, AMOLF, Saxion, TU/e, NHS, Harteraad, PHA, DCVA
Start date	M1
End date	M72

Objectives

We already have been successful in developing and validating several different prototypes of soft robotic hearts in the framework of a FET OPEN EU project (See section 6.2). Based on the lessons learned from this project, in WP1 a new generation of soft robotics actuators and sensor-integrated actuators miniature in size but with higher performance (high stroke, high output force, low fluidic consumption) for the HHH will be developed and integrated to reliably mimic cardiac movements. The arrangement and design of these actuators define the range of motions the HHH can perform. The pumping volume of the HHH can be optimized by, e.g., varying matrix design and material. The shape of the heart will be designed and tested, both in computational models to determine the optimal behaviour as well as in prototypes to test contraction patterns and pump function *in vitro*. For the latter, we will use Mock loop simulation set-ups that mimic the clinical situation. Essential in selecting the materials is the durability of the HHH; we, therefore aim for non-stretchable durable materials like woven durable fibers, proven to be durable in clinical use (e.g., aortic grafts). During the development of these (novel) materials, compatibility between the elastomeric matrix and the TE scaffold (WP2) will be optimized.

Objectives:

- To develop the soft functional component (actuators & sensors) of the soft robotic heart, that will provide the necessary cardiac output;
- To design and develop the soft robotic hybrid heart by utilizing the developed soft robotic components
- To develop a fabrication platform that can integrate the soft robotic comment in their desired location and orientation maintaining the HHH required flexibility and functionality
- To provide a modeling platform that can predict the response of the design to various physiological loading conditions and optimize the design based on the limitations and inputs of used materials, actuators, and sensors.
- To use our experimental platforms for mapping the cardiac output, pumping efficiency and durability of the soft robotic heart.

Methodology

we follow a loop of theoretical/experimental approach to design and develop new generations of high-performance soft robotic actuators, sensors, and sensor-integrated actuators. Since the performance of soft robotic components and systems directly depends to the characteristics of selected materials and their manufacturing techniques we also will investigate and develop the proper fabrication technique **(Tasks 1.1-1.3).** In **tasks 1.4 and 1.5**, we focus on the validation and selection of virtual and real developed prototypes. These tasks, in a loop with pervious tasks, create and iterative approach for achieving the most promising HHH design and prototype for the chronic in-vivo experiments before month 72.

Description of research activities

Task 1.1 Soft robotic prototyping for cardiac output (UT, EMC, AMOLF, Saxion) (M1–36). We will develop new generations of soft actuators, soft sensors, and sensor-integrated soft actuators. The actuators will be able to provide a large stroke and output force while consuming a small amount of fluidic pressure. Integration of fiber like sensors in the structure of these actuators enables us to monitor and control the actuator contraction. By customizing these components based on the requirement of HHH, we will develop different generations of prototypes of HHH and validate the required cardiac output at physiological pressures *in vitro*. The sensor integrated actuators and sensory fibers integrated in the structure of HHH will provide information for predicting heart deformations and output pressure. In a loop design of prototyping and validation, we will explore various approaches to build the matrix, and identify the optimal material properties, orientation, and density of soft robotic components and the geometrical features.

Task 1.2 Material selection and manufacturing (UT, EMC, TU/e, Saxion, TU Delft) (M1-48). We will investigate different fabrication techniques such as multi-material soft additive manufacturing, multi-step elastomer casting, computer-controlled textile fabrication and lamination, and in particular novel technique in 3D weaving/printing to embed the soft sensor-integrated actuators into the soft matrix of HHH prototypes. Experimental bench test experiments quantifying the mechanical consequences of these different fabrication techniques on the final matrix compliance and actuation will be integrated in the computational models in Task 1.3 and 1.4 - to extend the optimization design space.

In addition to the influence of each technique on the mechanical/fluidic performance of HHH, in collaboration with WP2, we also investigate the compliancy of each fabrication technique with living tissue formation techniques. In this step, we will identify the best combination of fabrication techniques to develop the HHH prototypes for large animal studies and identify a GMP-compliant manufacturer. Moreover, in collaboration with WP4 we ensure that the developed manufacturing technique can satisfy all the detailed requirements of HHH design, and can guarantee its durability and producibility for a batch production scenario. *Key performance indicator*: introduction of proper fabrication technique for HHH, fabrication platform for 3D fiber reinforced soft robots, selection

Task 1.3 Computational modeling coupling design choices to mechanical performance (TU Delft, UT, AMOLF, M1-M36). We will develop 3D fluid-structure interaction models of the HHH prototype to quantitatively capture the design's mechanical behavior under various hemodynamical loading conditions. More specifically, we will develop physics-based numerical models that integrate the prototype's fiber behaviour and braided matrix organization to compute the resulting physics-based range of motions of the full-scale prototype. The different physical prototype generations produced and experimentally tested in Task 1.1 will be used to calibrate and validate these computational models. *Key performance indicator:* high throughput in silico modeling framework to couple HHH design choices to its mechanical performance

Task 1.4 Selection of actuated ventricle technology (EMC, TU Delft, UT) (M36–48). Using the developed computational models in task 1.3 and the experimental validations in task 1.1, we will map the complete behavior of the actuated ventricle prototypes under various loading conditions. We will couple the 3D in silico models of Task 1.3 to analytical 0D models (lumped parameter networks) of the in vivo human cardiovascular circulation to study the HHH-body interaction under dynamic hemodynamical conditions that are difficult to recreate experimentally. We will perform systematic in silico studies on the combined effects of dynamic pressure loading, prototype shape and size, actuator arrangement, actuator design, matrix design and actuator/matrix materials (task 1.2) on the range of motions and mechanical performance of the respective HHH prototype. As a result, we will obtain a rich virtual population of HHH protypes where design choices can be effortlessly coupled to quantitative insights into the prototype's full cardiovascular performance. We will use this in silico prototype population to study cardiac output, efficiency, and left-right balance of the whole hybrid heart system with respect to dynamically changing and experimentally challenging physiological loading conditions. These insights will be used to inform design updates and decisions in further development phases, with the final goal to optimize the design of the actuated ventricle that provides the most suitable characteristics (WP0). *Key performance indicator:* optimization of prototype design with respect to full-body cardiovascular performance

Task 1.5 Finalization of HHH design (UT, EMC) (36-72). In month 36 we will deliver our first HHH prototype for the acute *in vivo* experiments and validation in WP5. To finalize the design for our chronic *in vivo* experiments in WP5, we collect inputs from *in vitro* and acute *in vivo* experiments and take them into consideration for modification of all the components, selected materials, and the design. This step will result in a design freeze before month 72. *Key performance indicator:* Finalized version of the developed HHH.

***Productive interactions (co-design and co-creation)**:*
The side-by-side collaboration of different expertise's in this WP ensures the integrability and reliability of developed solutions within the WP and its consecutive WPs.

- UT, EMC and AMOLF will design and develop soft actuators, fibrous sensors, and fabrication techniques to embed the components in the 3D shape of the designed HHH.. The requirement of these components will be also defined by the inputs provided by WP0.
- UT and UT/e will collaborate for guaranteeing the bio compatibility of the selected materials and fabricated fibrous structures.
- The performance of the developed HHH at UT will be evaluated by Mockloop testing at EMC and fluidic circuit characterization facilities at AMOLF.
- The in silico modeling framework of TU Delft will be specialized for the characteristics and specification of components and fabrication techniques at UT
- UT will collaborate with Saxion to guarantee the in lab and novel developed soft robotics components and fabrication techniques at UT are aligned with integration methods developed at Saxion and the HHH can be batch or mass producible.

***Contribution to project (impact)**:*

- Novel soft robotic components such as high-performance and sensor-integrated actuators will be introduced to the community of soft robotics. These components lead to a new generation of untethered soft robotics for different applications such as soft wearable/assistive robotics, surgical robotics, and sport science.
- A novel fabrication platform for the integration of smart fibers into the 3D elastomeric structures will be developed. In addition to the realization of HHH, the gained knowledge and fiber integration solutions can address a great need for the fabrication of complex fiber-reinforced structures for different applications such as prosthetics, implants, aeronaval components, etc.
- Modeling framework developed in this WP can guide to optimal design of HHH but it also can be utilized in modeling a big family of soft robotic systems. This is because fiber-reinforced soft fluidic structures are popular in the design of soft robotic systems.

Work package number	2
Work package title	Development of in situ tissue-engineered inner linings and valves
Work package leader	Prof. C.V.C. Bouten
Involved partners	TU/e, EMC, TU Delft, SBMC, AMOLF, Saxion
Start date	M1
End date	M72

***Objectives*:** To develop a bio-, immuno- and hemocompatible inner lining of the HHH to prevent adverse blood- and immune-related responses to the robotic heart; and to integrate in situ engineered heart valves in the robotic heart.

Methodology: To function effectively, durably, and safely, the HHH will be designed to prevent thrombosis and host-responses at the blood-material interfaces, such as endocardium and valves, while allowing adaptation of these structures to changing hemodynamic conditions. These challenges, common to cardiovascular implants, are best met by the use of living tissues – or mimics thereof – that reproduce the key bioactive, immunomodulatory, and anti-thrombogenic properties of the native heart. In this work package, material scientists, tissue-, bio-, and immuno-engineers join forces to equip the HHH with engineered living materials on the endocardial site and valves between the HHH and the native outflow tracts.
To this end, we aim to 'tissue engineer' (TE) a living endocardium and living valves directly *in situ*, i.e., inside the functioning implanted HHH by using immunomodulatory and regenerative materials that recruit cells from the patient's own bloodstream to grow new tissue. Building on our two decades of experience in this area, we propose the following approach:

- We will design, fabricate and test materials for the *in situ* TE inner lining and valves. This includes the generation of polymer scaffolds (e.g. via electrospinning) and/or coating with nano- or micro topologies (e.g. using nanoscribe or xolography) that will be tested regarding mechanocompatiblity (withstanding the deformations of the HHH), biocompatibility (including immune responses and blood compatibility), and neo-tissue formation under the hemodynamic conditions occurring inside the HHH; and the integration of these materials as scaffolds linked to the soft robotic matrix (with WP4).
- Because the creation of living tissue *in situ* will take time, we will design these materials such that they

i. are immunomodulatory, and anti-thrombogenic from the start. For the lining, we will make use of the soft robotic heart deformations and/or topological 'coatings' obtained with additive manufacturing, to prevent platelet adhesion and/or control protein adhesion. For valves, we will use porous electrospun scaffolds created from elastomeric materials **(Task 2.1).** Using computational modeling **(Task 2.2)** – supplemented with experiments **(Tasks 2.4-2.7)** – we will evaluate the risks of local platelet adhesion and thrombosis, such as to optimize initial material design.

ii. Promote homeostatic tissue growth by recruiting monocytic cells from the bloodstream to create a hemo-regenerative implant with durable lining and valves, covered by tissue/endothelial cells, also referred to as fallout healing. This includes the evaluation of (adverse) tissue remodeling and adaptation as well as the need for cell-driven material degradation once the endocardium is covered with a living lining and valves are completely cellularized.

- To calculate the stresses and strains transmitted from the active soft robotic heart to the endocardial and valvular structures and recruited cells and proteins, we will develop and use multi-scale computational frameworks **(Task 2.3).**
- Computed stresses and strains will be applied to material scaffolds with or without contact with blood **(Task 2.5)** and/or living cells **(Task 2.6)** under *in vitro* hemodynamic loading conditions using high-throughput experimentation **(Task 2.4).** Resulting optimized scaffolds will subsequently be tested under *in vivo* like conditions for the creation of endocardial lining **(Task 2.6)** or heart valve tissue **(Task 2.7).**

Description of research activities

Task 2.1 Acellular materials for inner lining and valves (TU/e, AMOLF, Saxion, SBMC) (M1–48). We will develop and use electrospun elastomeric materials (fiber diameter > 4 μm) as cell-free inner linings and valves, or coatings for immune-modulation, hemocompatibility, and cell recruitment, that can be safely, durably, and reproducibly coupled to the Holland Hybrid Heart (HHH) soft-robotic myocardium. We will follow a modular design approach where non-degradable base materials can be coupled to the myocardium and extended with additional (degradable) layers for optimal contact with blood, cell adhesion and subsequent monolayer and/or tissue formation in close interaction with Tasks 2.2-2.7. Additionally, we will develop and test coatings with (sub) micro-topology to maintain an antithrombogenic status of the endocardium. Specifically, we aim to design bio-inspired 'self-cleaning' surfaces that prevent platelet adhesion, leucocyte activation, and adverse immune responses to the material through continued change of the material surface via a combination of local corrugations and hemodynamics, like in native arteries. *Key performance indicator:* Library of materials and topological coatings for engineered living inner lining and valves.

Task 2.2 Computational modelling of thrombogenesis at the blood-material interface (TU/e) (M6-M30). A novel continuum model of platelet activation, aggregation, and essential regulators of the coagulation cascade will be used to describe transport and reaction of biochemical agonists and predict the risk of thrombus formation at the endocardial blood-material interface. We will adopt a recently developed numerical method that includes a biochemical model of intrinsic and extrinsic blood coagulation pathways associated with the complex biological processes following the changes in local mechanical stimuli due to heart wall motion and/or surface topology. Combining this computational model with *in vitro* modeling (**Tasks 2.4 & 2.5)** will allow us to first validate and next predict local thrombus formation in response to different surface coating / topology strategies; and hence to design a successful long-lasting anti-thrombogenic inner lining for the HHH. Our model will be unique in that it combines the initiation of platelet aggregation as a function of high shear rate flow fields, platelet receptor integrins, and conformationally-stretched vWF concentration, in response to local deformations and surface topology. It will include features from our previous deposited bounded platelet model, including shear induced platelet activation and embolization, as well as vWF conformational change in high shear rates, ADAMTS-13 to cleave vWF, and margination of large biomolecules such as leukocytes to account for inflammation that drives the coagulation cascade. *Key performance indicator:* Mapping the risk of thrombus formation at the endocardial blood-material interface.

Task 2.3: Multiscale computational modelling of force and strain transmission from the active soft robotic myocardium to the endocardial structures and valves (TU/e, TUD) (M6–45). We will develop 3D fluid-structure interaction models that accurately simulate the dynamic actuation and deformation of the Hybrid Heart ventricles. We will leverage these models to study the local and global mechanical behavior of the coupled endocardial structures, such as to later assess the influence of the mechanics on the endocardial lining during systematic *in-vitro* tests. Specifically, we expect that the endocardial structures will experience complex

local stretching and buckling patterns due to the transmission of actuation from the active soft robotics myocardium and intrinsic device-tissue stiffness differences. These deformation profiles can be beneficial for platelet repulsion, but detrimental for cell recruitment. Moreover, depending on implant design, positioning and hemodynamical flow conditions, valves will experience high strains in their leaflets as well as high shear stresses, mainly on the ventricular side which can drastically impact their longevity. By integrating and predicting all these biomechanical phenomena in one multiscale multiphysical (structural and fluid mechanics) computational framework, we will systematically guide the design of the soft robotics heart (with WP1 – Task 1.2) and optimize the used materials and coupling strategies to cooperatively enhance both mechanical efficiency and hemocompatibility.
Key performance indicator: Signature of local stresses and strains on endocardium and heart valves.
Task 2.4 High-throughput material testing under hemodynamic loading (TU/e, SBMC) (M1–M36). Using microfabrication and microfluidic technologies, we will develop a versatile in-vitro system to test the interaction between a library of materials and material topologies with cells and/or blood under pathophysiology mimicking conditions. The systems will allow the differential effect of shear stress and cyclic strain as well as the combination thereof, where parameters can be adjusted to mimic those in the Hybrid Heart myocardium. Readouts include acute and delayed immune responses, thrombogenicity, cytotoxicity, and functional monolayer and tissue formation and stability (see Task 2.5). *Key performance indicator:* High throughput *in vitro* platforms for cardiovascular materials screening.
Task 2.5 Blood-material interaction (TU/e, SBMC) (M1-M36). We will provide an extensive haemocompatibility profile of candidate materials, using sheep and human blood in parallel, ensuring translatability as we move towards *in vivo* clinical implementation of the HHH (WP5). Key parameters will include hemolysis, platelet activation, monocyte expression of tissue factor and other activation/adhesion marks, degradation of von Willebrand factor (vWF), microparticle accumulation and abundance/phenotype of endothelial progenitor cells.
Key performance indicator: heamocompatible and immunocompatible inner lining.
Task 2.6 Living endocardial lining (TU/e, EMC) (M36–72). We will evaluate cell recruitment and endothelial monolayer / tissue formation under haemodynamic conditions in order to establish a living lining for the Hybrid Heart endocardium. By modulating the host response to the foreign material, we aim to skew the immune response towards a favourable anti-inflammatory response. By using fibrous, degradable lining materials, recruited cells can produce their own flexible extracellular basal lamina, while the material degrades. In addition, we will target monocytic cells and endothelial progenitor cells to create a biological, non-thrombogenic cellular monolayer on top of the flexible lamina. *Key performance indicator***:** Living inner lining.
Task 2.7 Living cardiac valves (TU/e, EMC) (M36-72). Building on our proprietary knowledge on *in situ* TE heart valves, we will design electrospun micro fibrous-covered tri-leaflet heart valve scaffolds for unidirectional control of flow at the outflow tracts of the HHH. With input from Task 2.3, we will optimize valve and leaflet shape, as well as fiber orientations, such as to optimize endogenous cell recruitment, tissue formation and tissue mechanical homeostasis under HHH loading conditions. Efficacy and durability of scaffold designs will be tested using available commercial valve testers (BDC labs), while (monocytic) cell recruitment, tissue formation and remodeling, as well as scaffold degradation will be monitored using in-house developed valve bioreactors prior to *in vivo* testing (with WP 5). We will target scaffold materials with cell-driven enzymatic degradation profiles to ensure scaffold durability in case of suboptimal endogenous tissue formation.

Productive interactions (co-design and co-creation)

- Material scientists, tissue-, bio-, and immuno-engineers join forces to equip the HHH with engineered living materials
- Collaboration between computational experts and tissue engineers will synergistically lead to optimized designs of the inner linings for adequate blood-material interaction and prevention of thrombosis. To this end a smooth information flow between WP1, WP2, and WP4 is critical.
- Interaction with WP1 is essential for the assessment of force and strain transmission from the active soft robotic myocardium to the endocardial structures. Using computational models – in direct comparison with the in-vitro (WP2) and in-vivo experiments (WP5) of the project – allows us to assess and evaluate such forces over large ranges of heamodynamic conditions and for various HHH -designs.

Contribution to project (impact)

Scientific impact

- Beyond state-of-the-art integration of non-living and living engineered materials.
- Innovation at the cross road of materials science (NWA route “Materials -made in Holland” and cluster question #120: “Can we design smart materials and structures that have new and advanced properties?”)

and regenerative Medicine (NWA route "Regenerative Medicine: game changer moving to broad areas of application) through top-notch multidisciplinary science
- Novel in situ tissue engineering strategies
- In vitro screening platforms of cell-material and blood-material interaction
- Novel computational algorithms to predict tissue development and risk of thrombosis under hemodynamic loading conditions
- Polymeric and living interfaces for optimized blood-material interaction

Societal impact
- The creation of a living engineered tissue that grows *in situ* will facilitate clinical implementation as compared to providing the HHH with a living lining prior to implantation. A cell and tissue free HHH at time of implantation complies with current regulations for medical devices and poses less complex regulatory, ethical, and fabrication constraints on the device.
- Contribute to the current standards tests and knowledge with respect to EU directive on medical devices (MDR) and regulatory frameworks for absorbable materials in the body (e.g., ISO/TS 37137-1: 2021)
- SBMC: strengthening its portfolio on screening cell-material interactions for medical purposes, including regenerative medicine, and in particular the often-overlooked effects of large deformations in combination with cells and blood on material performance (degradation, durability, regenerative potential, etc.). Expertise that also will finds its application in other therapies.
- High-throughput in vitro material testing: the acquired systems can be used to prioritize materials and obtain crucial initial information prior to *in vivo* testing, thus reducing and refining the use of animal models.

Work package number	3
Work package title	Controlling & Monitoring HHH behavior
Work package leader	Bas Overvelde
Involved partners	AMOLF, UT, Saxion, Trailblazers
Start date	M1
End date	M72

Objectives

In WP3 the focus lies on controlling and monitoring the beating of the HHH. Fluidic circuits will be used to transform a continuous inflow from a hydraulic pump into pulsating output that will activate the soft robotic muscles in the heart. The circuits will be designed to passively adapt to variations in the physiological conditions, without the direct need for electronic sensing. Besides passively controlling the heartbeat, we will incorporate soft sensing fibers within the soft matrix to monitor deformation and provide feedback to optimize motile behavior during the development process of the HHH. By comparing this data to pressure and flow measurements performed at the side of the fluidic circuit, we will be able to determine the minimal requirement to identify proper functioning of the HHH and potential problems occurring during operation. The sensor data from the HHH will be transmitted from inside the body and analyzed in the cloud in order to provide stakeholders (e.g. patients and doctors) with insight on the performance of the heart. The main objectives in WP3 are:

- To build hydraulic circuits containing soft components to passively control the beating of the HHH.
- To identify essential tests and sensors to determine the performance of the HHH under varying physiological conditions.
- To model the behavior of the fluidic circuit and HHH under different physiological conditions in a system model.
- To determine the most accurate way to monitor the performance of the HHH during prototyping.
- To determine the most reliable way to monitor the performance of the HHH upon chronical implantation.
- To build a hardware and software platform to provide information on the performance of the HHH.

Methodology

The methods used in WP3 can be best divided in two parts, control and monitoring.

Control

- To enable a heartbeat in the HHH that passively adjusts to changing physiological conditions, and with the aim to make a device that is as soft, durable and efficient as possible, we will be employing so-called soft fluidic circuits[35]. In previous work, we have developed pneumatic circuits with soft valves

that can transform a constant flow a pump into a pulsating flow. This pulsating flow can be used to power a soft actuator, and thus effectively create a heartbeat in the HHH. **(Task 3.1, 3.2)**

Monitoring:

- To monitor the behavior of the device (not to provide feedback for control), we will follow two directions in parallel. First, we will be using pressure and flow data obtained from the fluidic circuit to infer the performance of the heart. Second, we will incorporate smart fibers into the soft matrix to characterize the deformation of the HHH prototype. Depending on the durability and reliability of the fibers, these will be used in the development phase and in the final device (only if proven reliable and durable enough). These smart fibers have already been incorporated previously in textiles[36] **(Task 3.3, 3.4)**
- For the chronical animal experiments, we will develop custom hardware and software to build an interface for researchers, surgeons and patients to monitor the behavior of the heart. Not only do we aim for the best way to demonstrate the data (and determine which data is best to show), we will also provide analytical tools (E.g. AI) that automatically interpret the data to look for trends (e.g. long-term performance evaluation). **(Task 3.5, 3.6, 3.7)**

Description of research activities

Task 3.1 Develop hydraulic fluidic circuits for passive control of the HHH (AMOLF) (M1-M36). In order to cyclically activate the fluidic muscles in the HHH, we will employ soft hydraulic circuits that passively generate a pulsating flow when provided with a constant flow or pressure input from a hydraulic pump. Based on the blood pressures inside the HHH (which depend on physiological conditions), these soft hydraulic circuits will passively adjust their behavior (e.g. increase heart rate, or increase stroke volume). *Key performance indicator:* soft hydraulic circuits passively create and adjust heart rate/ stroke volume.

Task 3.2 Develop a system model to simulate the interactions between fluidic circuits, HHH, and varying physiological conditions (AMOLF) (M1-M48). In order to design a fluidic circuit that is capable of passively adjusting to changing physiological conditions, we will develop a system model using the electronic-fluidic analogy. We will use measured data from the HHH obtained in WP1 in our simulations. We will further validate the model by comparing the results with mock-loop experiments performed in WP4. *Key performance indicator:* developed and validated system model.

Task 3.3 Incorporate pressure and flow sensors into soft hydraulic circuit to predict performance of the HHH (AMOLF) (M24-M48). In order to monitor the behavior of the HHH, it would be ideal to be able to indirectly, but continuously, estimate the blood pressure and flow to characterize the performance of the HHH. We will explore if, and how, measuring the pressures and flows in the fluidic circuit allows us to accurate predict the performance of the HH. *Key performance indicator:* soft hydraulic circuit contains pressure and flow sensors

Task 3.4 Predicting HHH deformation and actuators performance based on the soft sensory fiber (UT) (M24-M48). In WP1 soft fiber sensors based on capacitive and resistive sensing will be developed, characterized, and integrated in the body of HHH and the actuators' structure. In this task we will investigate if these soft sensory components can predict correctly the performance of the HHH, and importantly how well they predict the local deformations on the surface of the HHH that is in contact with blood and living cells/tissues. We also investigate the minimum number of soft sensors and their orientation for the proper monitoring of heart behavior. *Key performance indicator:* optimum number and orientation of soft sensors determined.

Task 3.5 Build hardware and software to monitor HHH behavior for *in vivo* and *in vitro* experiments (Saxion) (M1-M48). In order to read out the sensors used to monitor the performance of the heart, hardware and embedded software will be developed that can wirelessly transfer the data to devices outside the body, or even directly to the cloud. *Key performance indicator:* Developed and validated hardware and software.

Task 3.6 Develop cloud software for chronical experiments (Trailblazer) (M24-M60). To provide information on the HHH's behavior, an online cloud-based platform will be developed for researchers, doctors and patients. This will be a state of the art software platform for monitoring and distributing relevant information from the HHH in a secure, reliable and controlled way to medical experts, the relevant research community and patients such that each has easy but secure access to the information, adopted to their particular needs. Therefore, this platform will be develop in close cooperation throughout the development process with representatives of researchers, doctors and patients to assure that their needs are properly collected and implemented. *Key performance indicator:* Developed and validated cloud software.

Task 3.7 Develop algorithms and performance indicators to evaluate long-term performance of the HHH (AMOLF, Trailblazer) (M36-M84). To be able to continuously monitor the HHH and identify potential problems, we will develop algorithms (e.g. based on AI) that will interpret the data to look for changing trends, e.g. to evaluate changing physiological conditions of the patients, or degrading performance of the device.

Key performance indicator: Developed and validated algorithms for long-term evaluation of HHH performance

Productive interactions (co-design and co-creation)

Development of the fluidic control circuits and embedded sensors in these circuits will be done by AMOLF, including the model of the integrated system. As an additional way to monitor the HHH, UT will explore how to embed smart fibers directly in the HHH, which will be compared to sensing results obtained with the fluidic circuits developed by AMOLF. The sensors provided by both AMOLF and UT will be integrated with the hardware and (cloud)software provided by Saxion and Trailblazers. This software will provide the basis for AMOLF to develop the algorithms that will continuously monitor the performance of the HHH.

Contribution to project (impact)

In WP3 the approaches to control and monitor the HHH will be developed, which is an essential component of the HHH development. Several approaches to monitor the heart will provide the much-needed information and performance indication for researchers during development, but also to doctors and patients during operation. Continuous monitoring (through specialized algorithms) will also enable the identification of potential problems in the HHH, which is essential for future implantation and for the safety of patients.

Work package number	4
Work package title	System integration
Work package leader	Saxion MT
Involved partners	Saxion ID, Saxion SFT, TU/e, AMOLF, UT, EMC
Start date	M7
End date	M72

Objectives

The focus of WP4 is the systematic and the continuous integration of the subsystems developed in the previous three WPs (WP1-WP3) into a singles HHH system**.** This WP also includes a rigorous testing of the functionalities and durability of the HHH *in vitro*, using an advanced isolated, pulsatile mock loop platform. All components of the soft robotic heart and the TE scaffolds will be integrated and bio- and hemocompatibility will be validated. The objectives of this WP include:

- Developing relevant test environment;
- Designing a series of critical tests to verify functionalities and durability of HHH as defined in WP0;
- Integrating the individual subsystems developed in WP1-WP3 into a complete HHH proof-of-concept device;
- Evaluating the performance of the integrated device and fine-tuning it to meet the system requirements defined in WP0.

Methodology

Systems engineering: as already mentioned in WP0, system engineering approach is used for systematically designing a complex and multidisciplinary systems such as the HHH. In addition to the designing process, this approach also prescribes how to meticulously assemble components and subsystems to realise a fully functioning system that meets the user requirements. In particular in this WP4, we will use Decomposition-Composition thinking. It is a formal logic and process of determining what happens when a function splits[34]. This helps to identify what additional interfaces are created and to check their consistency and traceability. To that end, we elaborate the integration and testing plan in T4.1 based on the outcome of WP0 and the new insights obtained in WP1-WP3. The integration and testing in T4.2 involve continuous and iterative process that will start as soon as (even partial) subsystems from WP1-WP3 are available. This approach will provide new insight at the earliest time possible. This will also ease the integration process and saves time at a later stage. The integration and testing processes and results will be well documented in T4.3 to track the progress as well as to use it as input for the subsequent iteration of HHH integration.

Description of research activities

Task 4.1: Elaborate plan for integration and Testing (Saxion, EMC, AMOLF, UT, TU/e) (M7-M18). This task analyses the user and system requirements in WP0 and acts a guideline for iterative integrations. The integration process will involve several intermediate releases to cope with possible changes in WP1-WP3. As such, this task will run in parallel with the development of the (sub)systems (WP1-3) so that their integration is planned as soon as subsystems are ready. This tasks also includes the preparation of elaborate test plan and identification of functional and technical performance indicators. These indicators will be used in task 4.3 to

evaluate of the performance of each integrated HHH release. *Key performance indicator:* Continuous integration and testing plan.

Task 4.2: Integration and Testing (Saxion, AMOLF, UT, TU/e, EMC) (M13-M54). This task focuses on continuously integrating the subsystems developed in WP1-WP3, and rigorously testing the integrated HHH system. The integration is organized in five integration cycles (once per year for five consecutive years). Each integration cycle consists of an integration week, in which all consortium partners bring their latest subsystems, integrate and test. As such, possible issues arising from hardware and software incompatibilities among the various subsystems will be identified and mitigating action will be taken in time. *Key performance indicator:* 5 releases (1 each integration cycle) of the HHH PoC.

Task 4.3: Evaluation and fine-tuning (Saxion, EMC, UT, M51-M72). This task focuses on evaluation of the functional and technical performance of the HHH system integrated in Task 4.2 based on the evaluation metric developed in Task 4.1. The evaluation results of each integration cycle will be used as input to fine-tune the integrated system. While minor adjustments will be addressed during the on-going integration week, major adjustments will be used as guidelines to improve each subsystem in WP1-WP3 in the next iteration and will be addressed in the next integration week. *Key performance indicator:* 5 releases (1 each integration cycle) test reports.

Productive interactions (co-design and co-creation)

The integration of the various technologies developed in WP1-WP3 will be coordinated and mainly carried out by Saxion. The partners involved in the development of the soft robotics components (UT, EMC, TUDelft, AMOLF, Saxion, TU/e), the in situ tissue-engineered inner linings and valves (TU/e, EMC, TU Delft Alliance, SBMC, AMOLF, Saxion), and the Controlling & Monitoring HHH behavior (TU/e AMOLF, UT, Saxion, Trailblazers) will contribute to the hardware and software integration of their subsystems.

Contribution to project (impact)

The integration of all parts into a working hybrid heart has never been done before. The successful integration of a functional HHH will have a paramount impact on revolutionizing the current transplant treatment.

Work package number	5
Work package title	Proof of concept in large animal model
Work package leader	EMC
Involved partners	All partners, UMC Utrecht and Medanex as subcontractors
Start date	M1
End date	M84

Objectives

- To generate proof-of-concept data in a large animal model; to demonstrate the safety and performance.

Methodology

- Filing animal ethical documents, in order to obtain approval for in-vivo experiments **(Task 5.1)**
- Chronic in-vivo implantation of heart valves in orthotopic position by open-heart surgery with cardiopulmonary bypass in large animals **(Task 5.2)**. This will provide information on the functionality of the heart valves, later to be used in the prototype artificial heart.
- Acute in-vivo implantation of the prototype in large animals, by open-heart surgery with cardiopulmonary bypass **(Task 5.3).** This will provide information on the best working prototype.
- After choosing the best prototype, chronic in-vivo implantation of the prototype in large animals will be conducted, by open-heart surgery, removal of the native heart and weaning from cardiopulmonary bypass **(Task 5.4)**.
- Conducting chronic in-vivo trials in large animals in GLP facility **(Task 5.5)**. These results will comply with FDA regulations and are required to proceed to FDA approval of the total artificial heart.

Description of research activities

Task 5.1 Design of *in vivo* studies, ethics and regulatory requirements (EMC, Medanex) (M1-M36). In this task, the study design and outcomes of the *in vivo* studies will be identified to ensure the final data package generated will comply with regulatory requirements from the FDA/selected notified body. Before the start of the studies, ethical approval for animal testing will be obtained at all participating centres according to national and European guidelines.

Task 5.2 *In vivo* testing of heart valves in sheep (EMC, TU/e) (M1-M36). Validation/testing of high pressure (aorta and mitral) and low-pressure (pulmonary and tricuspid) heart valves by the AMC team. In total, 4 different prototype heart valves will be validated using a 6 months follow-up initially (n=10 per group) and ultimately a 1-year follow-up (n=10).
Task 5.3 Acute *In vivo* implantations in large animals from prototype to design freeze (EMC, partners from WP1-4) (M37-M72). Assess the device performance of prototypes developed and assembled in WP 1-4: 1) Fitting studies in large animals by CT scan and cadaver try-outs; Acute extracorporeal implantations (~3-5 per prototype) to assess the performance of the device on cardiac output and generated blood pressure; 2) Acute intracorporeal implantation in large animals (~3-5 per prototype). Implantations will take place at the animal facility (GDL) at UMC Utrecht.
Task 5.4 Chronic *In vivo* implantations in large animals (EMC, Medanex) (M60-M84). 1) Based on the results of the acute intracorporeal studies, we will choose 1 prototype to test during chronic implantations in large animals. We will use the optimized prototype to test in chronic large animal procedures in which the chest is closed and the animal is weaned from cardiopulmonary bypass and the ventilator. The first chronic implantation in large animals will have a FU time as long as possible; 2) Chronic non-GLP validation in large animals (max 15 animals) with a 3 months follow-up. All implantations will take place at the preferred contractor (Medanex) and will be performed by Prof. Kluin and her team.

Productive interactions (co-design and co-creation)
The *in vivo* studies will be carried out at Utrecht UMC and Medanex with Prof. Jolanda Kluin performing the surgeries. The first *in vivo* testing will be performed with TU/e to validate the performance of the developed valves. Acute studies using the integrated HHH prototype will be performed with all partners from WP1-4 to improve the HHH before its final chronic *in vivo* validation at the end of this project.

Contribution to project (impact)
- New soft elastomeric heart valves can be used as better alternatives to the current prosthetic valves. This is especially important in the current era of transcatheter heart valve implantation for which the heart valves need to be flexible. These valves are potentially durable, cost-effective, and applicable in low-income countries.
- In vivo studies with the developed total artificial heart prototype provide important information on the artificial heart's functionality, durability, biocompatibility, potential adverse events etc., which cannot be obtained by *in vitro* work only. These results will have impact on the current available treatment limited treatment options of patients suffering from end-stage heart disease, and will give this patient group new perspective on receiving life-saving treatment.
- In addition, results obtained by chronic *in vivo* trials, may revolutionize the field of transplantation medicine in general, highlighting the use of a scalable soft biocompatible artificial organ in chronic animal trials. It will form an essential basis for a completely new field of scientific and technological research that integrates soft robotics and electrical engineering with TE. Soft robots may allow development of various biologically inspired artificial organs and limbs.

Work package number	6
Work package title	Business strategy & regulatory approval & knowledge dissemination
Work package leader	K M Veen (EMC)
Involved partners	EMC, EVOS, Streefland, DCVA, NHS, Harteraad, PHA
Start date	M1
End date	M84

Objectives
- To ensure regulatory approval and knowledge dissemination and secure IP and exploitable results
- To ensure sustainability of the project beyond the preclinical testing phase

Methodology
- To file the technical dossier in accordance with current regulations
- To provide a framework for IPR and legal management
- To monitor and secure IP and exploitable results of the project
- To ensure financial sustainability supporting the Holland Hybrid Heart development
- To support knowledge dissemination to involved stakeholders

Description of research activities

Task 6.1: Technical dossier filing according to current regulations (EMC, EVOS) (M1-M84). The HHH team is very much aware of the regulatory requirements for chronic preclinical in vivo and first-in-human studies and beyond. Considering the risk and type of the novel device and development timelines we will consider applying to the MHRA for exceptional use of non-complying medical devices. EVOS has prior experience with this scenario and will evaluate feasibility and guide approval. For subsequent clinical use, next to extremely valuable clinical and biomechanical/biocompatibility information, the compassionate use scenario will allow us to better position the regulatory clinical study towards market entry. For first-in-man use (beyond the 7-year HHH project) a near full Technical Dossier will be required, including the Risk Management Plan & Report, Investigator's Brochure, Preclinical Testing Plans & Reports. The HHH will likely be classified as a Class III Medical Device according to the current relevant EU MDR regulation.

Task 6.2: Business strategy development and sustainable financing (EMC, EVOS, DCVA) (M1–84). The consortium will establish a private company (referred to as 'NewCo') that shall hold all relevant IP rights, secure additional financing, and lead commercial negotiations. The establishment of one legal entity that holds all IP rights will facilitate attracting additional sources of dilutive and non-dilutive funding to support further preclinical and clinical development. Such legal entity will be an appropriate partner for the discussions and negotiations with large medtech companies. Initially all shares in NewCo will be held by a Foundation that will be established at the same time as NewCo. In collaboration with involved TTOs we will develop an investor-ready business plan that NewCo will use as a starting point for securing funding and exploiting the project results which is an essential step towards implementation.

Task 6.3: Intellectual Property management and legal (EMC, EVOS) (M1–84). A formal consortium agreement will be signed detailing agreements on background and foreground IP as relevant. Budget is reserved for developing the HHH IP portfolio with the assistance of legal and patent officers. We will create a framework for the monitoring, timely identification, protection and exploitation of the innovation outcomes of the project, through an Innovation Management System (IMS). IP, competition, end-users, and societal expectations surveys will be performed to back IP management and define the competitive advantages specifications. In addition, we will monitor exploitable results through surveys of project's Exploitable Results; b) performing due diligence on freedom to operate, prior art search and patentability study, regulatory and market adoption barriers, competition mapping. The medical support technology office of Erasmus MC will be consulted for advice on MDR compliance.

Task 6.4 Knowledge dissemination and communication (Streefland, DVCA, EMC, NHS, Harteraad, PHA) (M1-84). The obtained knowledge will be disseminated among scientific stakeholders in peer-reviewed publication. For wider knowledge dissemination we will work together with the science journalist and communication expert Susanne Streefland, who will develop a social media strategy, generate content and publish articles for the wider public. At Erasmus MC we will organise a conference for all stakeholders, including patients in the middle and at the end of the project to inform them of our progress. Susanne Streefland will inform the public including government organizations.

Productive interactions (co-design and co-creation)

WP6, the interaction of EMC with co-funders Evos, DCVA and cooperation partner Susanne Streefland is needed to not only prepare for regulatory approvals (expertise EVOS), and establish a private company (TTO EMC, DCVA, EVOS), but to also disseminate the knowledge among stakeholders. All partners within this WP bring unique expertise that is needed to reach the objectives.

Contribution to project (impact)

The dynamic Innovation Management System (IMS) will set-out the major goals, the structure, the supporting tools and the monitoring indicators of the RD&I process. The process will be qualified through instruction and implementation of the standard NP 4457. Implementation will enable support and coordination amongst consortium members regarding management of the project's innovation outcomes, including exploitable results, IP and business plan/go-to-market plans. Dissemination and communication will ensure that all stakeholders, required to achieve societal impact, are informed.

7.3 Risk management and contingency plan

Risk Description	Category	Mitigation and Contingency
Reliability and durability of soft actuators components is not sufficient	Scientific	**Mitigation:** Identify the source of failures and engineer the single components separately in order to improve long-term reliability. Build a setup to test durability, use simulations to predict deformations. Reduce high stress regions, and select materials accordingly. **Contingency:** Substitute with customized commercially available components and re-enter the development cycle.
Right/left balance is not automatically adjusting	Scientific	**Mitigation:** Mimic stiffness of the natural heart more precisely and/or include regulation in fluidic circuit. **Contingency:** Re-enter the development cycle.
Living endocardial lining is unsuccessful	Scientific	**Mitigation:** Requirements for living endocardial lining are assessed in detail. **Contingency:** We will concentrate on a non-living lining that is anti-thrombogenic and immune compatible, starting from robust/non-degrading biocompatible materials.
Creation of living valves is unsuccessful	Scientific	**Mitigation**: Establishing requirements for living valves and working towards our goal in iterative steps. **Contingency:** We will use commercially available, non-living valves.
Fluidic circuit does not provide enough power	Scientific	Problem could be due to high internal friction. **Mitigation:** redesign circuit, **Contingency:** use air instead of fluid. Problem could be efficiency. **Mitigation:** redesign circuit to be more efficient, **Contingency:** use driveline. Problem could be not enough power. **Mitigation:** use larger pump, **Contingency**: use driveline.
Monitoring fluidic circuit does not provide enough information in performance of HHH	Scientific	**Mitigation:** add more sensors, or combine with textile sensors. **Contingency:** Measure blood pressure and flow.
Textile sensors not durable enough	Scientific	**Mitigation:** redesign, and use data from FEM simulations to predict wall deformation. **Contingency:** Only use data from fluidic sensors.
Connection and surgery of the HHH in large animals is technically more challenging than anticipated.	Scientific	**Mitigation**: using gained experience in previous projects. **Contingency:** calves can be used as alternative animal model.
Complications of the HHH such as bleeding, low cardiac output.	Scientific	**Mitigation:** Computational modelling, mock-loop testing, biocompatibility studies and acute *in vivo* studies are used throughout the R&D process to minimize the chances of complications. **Contingency:** HHH components reenter the development cycle.
Delay in project progress and/or deviations in budget.	Financial	**Mitigation:** The comprehensive work plan has been discussed to ensure its feasibility in terms of the proposed timelines and budget. Active and dedicated project coordination is implemented to closely monitor progress and expenses, allowing for early identification of issues. **Contingency:** Restructure progress planning and look for investors.
Clinicians/Patients won't accept HHH as treatment option	Societal	**Mitigation:** Clinicians and patients are both involved in the development of the HHH to ensure that their needs are met. Meetings and press releases are used to keep stakeholders informed. **Contingency:** Further meetings ae organized to answer all outstanding questions. Trainings for clinicians can be offered.

7.4 Justification of project budget

Budget range [A]	
Budget range requested budget	☐ 0.5 – 2 M€ ☐ 2 – 5 M€ ☒ 5 – 10 M€

Budget division per cost type

- **Personnel costs** add up to €7.9M (including 13 PhD students, 6 postdocs and benchfees)
- **Material costs** add up to €1.8M
  Justification: The material costs are exceeded by 804k due to high costs of animal experiments (914k). We planned the animal experiments according to 3R principle (Replacement, Reduction and Refinement), thus using the minimum number of animals to achieve meaningful results. These animal experiments are essential to test and validate the HHH performance *in vivo*. Without these experiments, the next step to a first implant in humans cannot be taken.
- **Other costs include:** Accommodation costs of €70k; Knowledge utilization costs of €500k; Project management costs of €353k.

Budget division per partner

Each co-applicant is allocated a share of 7%-34% (personnel costs) of the budget. The highest budgets are allocated to Erasmus MC (€2.6M) for key role in three work packages (0, 1 and 5). A detailed overview of all costs per partner is provided in the budget annex.

8 Data management & ethical aspects

8.1 Data management

1) Will this project involve re-using existing research data?
☒ *Yes: Are there any constraints on its re-use?* The consortium partners have access to own datasets that can be made available for re-use. Potential limitations for re-use may be dependent on the constraints present on the informed consent forms, this may differ per dataset.
☐ *No: Explain briefly why. Have you considered re-using existing data but discarded the possibility?*
2) Will data be collected or generated that are suitable for reuse?
☒ *Yes: Please answer questions 3 and 4.*
☐ *No: Please explain why the research will not result in reusable data or in data that cannot be stored or data that for other reasons are not relevant for reuse.*
3) After the project has been completed, how will the data be stored for the long-term and made available for the use by third parties? Are there possible restrictions to data sharing or embargo reasons?
Research data will be stored following existing protocols and infrastructure at the UMCs and Universities of Technology participating in the proposed consortium. An experienced data manager will maintain the database and check the information in the database for completeness, consistency and plausibility. FAIRness of the data will allow accessibility and re-use of the data. The Data Management plan will describe the protocols and authorizations necessary for that access.
4) Will any costs (financial and time) related to data management and sharing/preservation be incurred?

☐ *Yes: Then please be sure to specify the associated expenses in the budget table of this proposal.*
☒ *No: All the necessary resources (financial and time) to store and prepare data for sharing/preservation are or will be available at no extra cost.*
Research data will be stored secured and safely as described above on the servers of the different co-applicants. Long-term storage facilities for biomaterials (i.e. refrigerators, freezers) are available at every department working in this project.

8.2 Ethical aspects

	Not applicable	Not yet applied for	Applied for	Received
Approval from a recognised (medical) ethics review committee*	☐	☐	☒	☐
Approval from an animal experiments committee*	☐	☐	☒	☐
Permission for research with the population screening Act*	☒	☐	☐	☐

** If applicable, proof of approval will need to be sent to NWO before the start of your project*

9 Statements by the main applicant

9.1 Other grant applications

Title proposal	A Framework to Increase the Durability and Efficiency of a Soft Robotic Heart
Applicant(s)	Bas Overvelde
Funding agency and call	NWO, Vidi
Budget applied for	800 keuro
Date of submission	11-10-2022
Estimated date of decision	End of June 2023
Difference with this proposal (percentage)	95%
Describe the difference	While the topic is somewhat similar, the aim of the proposal is to develop an alternative modular framework for fabricating and testing soft robotics, with a Soft Robotic Heart as demonstrator. No full integrated system will be developed, and no animal studies will be performed. By all means, such an alternative strategy could strengthen the soft robotics component of the HHH proposal.

9.2 By submitting this form I declare that:

☒ The main applicant is appointed at their host institute for the duration of the application process and for the project that is applied for.

☒ I, and all individuals and parties involved in this proposal, satisfy the nationally and internationally accepted standards for scientific conduct as stated in the *Netherlands Code of Conduct for Research Integrity 2018* (Universities of the Netherlands).

☒ I have discussed the final version of this proposal with all individuals mentioned in this proposal as (intended) consortium partners. All such individuals mentioned are aware of and agree with their role and intended contribution to the project, should this be awarded funding.

☒ All consortium partners mentioned in this proposal, especially the co-funders, have taken notice of the rules for this Call for proposals on Intellectual Property and publication (see section 5.1.6 of the call for proposals), including the conclusion of a project agreement between all consortium partners before the start of the project.

☒ I follow the NWO policy on data management.

☒ I have completed this application form truthfully.

Name main applicant: Jolanda Kluin

Place: Rotterdam

Date: 24.01.2023

Before you submit the full proposal in ISAAC you will be asked to confirm again that you have completed the form truthfully.

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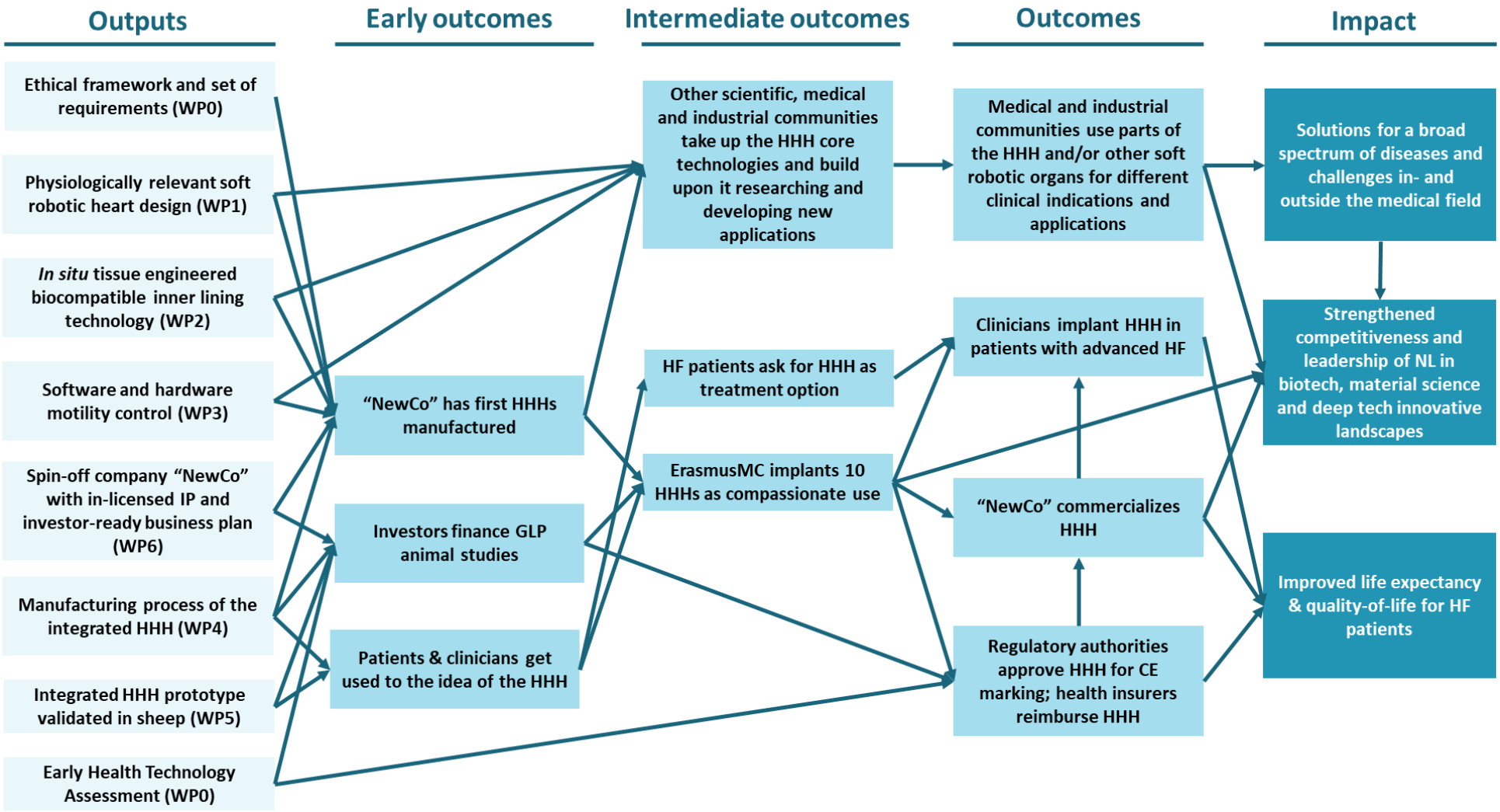
Annex 1A: Pathway Diagram



Annex 1B: Impact pathway indicators

Output	Indicator
Output1: *Ethical framework and set of requirements*	• Documents/study results indicating stakeholders needs (M0-84)
Output 2: *Physiologically relevant soft robotic heart design*	• Develop new generations of soft actuators, soft sensors, and sensor-integrated soft actuators (M36). • Durable material selected (M48) • Computational model for cardiac output established (M36) • Actuated ventricle technology established (M48) • HHH design finalized (M72)
Output 3: *In situ tissue engineered biocompatible inner lining technology*	• Library of materials and topological coatings for engineered living inner lining and valves (M48) • Mapping the risk of thrombus formation at the endocardial blood-material interface (M30) • Signature of local stresses and strains on endocardium and heart valves (M45) • High throughput *in vitro* platforms for cardiovascular materials screening (M36) • Heamocompatible and immunocompatible inner lining (M36) • Living inner lining (M60). • Living heart valves for HHH (M72)
Output 4: *Software and hardware motility control*	• Developed soft hydraulic circuits (M36) • Hardware and software platform for performance testing established (M48)
Output 5: *Spin-off company "NewCo" with in-licensed IP and investor-ready business plan*	• Dutch spin-off company (NewCo) established (M84) • Licensing agreements signed (M84) • Detailed business plan (M84)
Output 6: *Manufacturing process of the integrated HHH*	• Material selection and manufacturing processes finalized (M48) • HHH prototype test environment (M18) • 5 proof-of-concept HHH over the course of the project (M72) • Test reports about HHH prototype performance (M72)
Output 7: *Integrated HHH prototype validated in sheep*	Acute and chronic (3 months) validation in sheep performed using the following criteria: • Acute: Fitting, cardiac output, generated blood pressure (M39-M75) • Chronic: survival (M75-M84)
Output 8: *Early Health Technology Assessment*	• Established and validated eHTA model (M48)

Outcome	Indicator
Outcome 1.1: *Medical and industrial communities use parts of the HHH and/or other soft robotic organs for different clinical indications and applications*	Devices or technologies based on the HHH core technologies (or containing parts of the HHH) enter clinical practice for indications beyond advanced HF, or industrial applications outside the medical field
Outcome 1.2: *Clinicians implant the HHH in patients with advanced HF*	- Increase in HHH transplants - HHH is expected to replace current biventricular assist device, nevertheless may be beneficial in up to 44% of current left ventricular assist devices (LVAD), as these patients will develop late right ventricular failure, the Achilles heel of current LVADs - If better quality of life is achieved than with current LVADs, HHH will be implanted in patients with LVAD indication
Outcome 1.3: *'NewCo' commercializes HHH*	Distribution agreement in place and first sale is a reality
Outcome 1.4: *Regulatory authorities approve HHH for CE marking; health insurers reimburse HHH*	CE-marking and/or FDA approval in place. HHH incorporated in health insurance policies
Intermediate outcome 2.1: *Other scientific, medical and industrial communities take up the HHH core technologies and build upon it researching and developing new applications*	Publications with novel findings citing HHH core technologies being applied in other indications or applications
Intermediate outcome 2.2: *HF Patients are asking for a HHH as treatment option*	Patients proactively asking about the HHH as a treatment option
Intermediate outcome 2.3: *Erasmus MC cardiac transplant teams are allowed and willing to implant the HHH in up to 10 patients as compassionate use*	HHH implanted in 10 patients (as compassionate use); Datasets on outcome measures available and published
Early outcome 3.1: *"NewCo" has first HHHs manufactured*	Material selection and manufacturing processes finalized; 10 GLP-compliant HHHs manufactured
Early outcome 3.2: *Investors finance Good Laboratory Practice (GLP) animal studies that result in approval for first-in-man studies*	NewCo secures funding round to finance GLP studies GLP studies are successful
Early outcome 3.3: *Patients, relatives and clinicians get used to the idea of having a soft robotic total artificial heart*	High interest and participation in surveys; positive attitude measured in surveys

Annex 2: Project overview

WP			Partner	Year 1				Year 2				Year 3				Year 4				Year 5				Year 6				Year 7			
				Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
0	**WP0**	**Safeguarding impact for HHH**	**Saxion**																												
	Task 0.1	Interface analysis	Saxion																												
	Task 0.2	Translation to system requirements and architecture	Saxion (ID, MT, SFT), EMC, UT, TU/e. Trailblazer, UM																												
	Task 0.3	Ethical Parallel Track	All																												
	Task 0.4	Scenario-based Design	Saxion, EMC																												
	Task 0.5	eHTA	EMC																												
1	**WP1**	**Development of soft robotics components**	**UT, EMC**																												
	Task 1.1	Soft robotic prototyping for cardiac output	UT, EMC, AMOLF, Saxion																												
	Task 1.2	Material selection and manufacturing	UT, EMC, TU/e, Saxion, TU Delft																												
	Task 1.3	Computational modeling to study cardiac output under various physiological conditions.	UT, EMC, TU Delft, AMOLF																												
	Task 1.4	Selection of actuated ventricle technology	UT, EMC, TU Delft																												
	Task 1.5	Finalization of HHH design	UT, EMC, Haarteraad, DCVA, PHA																												
2	**WP2**	**Development of in situe tissue-engineered inner linings**	**TU/e**																												
	Task 2.1	Acellular materials for inner lining and valves	TU/e, AMOLF, Saxion, SBMC																												
	Task 2.2	Computational modelling of thrombogenesis at the blood-material interface	TU/e																												
	Task 2.3	Multiscale computational modelling of force and strain transmission from the active soft robotic myocardium to the endocardial structures and valves	TU/e, TU Delft																												
	Task 2.4	High-throughput material testing under hemodynamic loading	TU/e, SBMC																												
	Task 2.5	Blood-material interaction	TU/e, SBMC																												
	Task 2.6	Living endocardial lining	TU/e, EMC																												
	Task 2.7	Living cardiac valves	TU/e, EMC																												
3	**WP3**	**Controlling & Monitoring HHH behavior**	**AMOLF**																												
	Task 3.1	Develop hydraulic fluidic circuits for passive control of the HHH	AMOLF																												
	Task 3.2	Develop a system model to simulate the interactions between fluidic circuits, HHH, and varying physiological	AMOLF																												
	Task 3.3	Incorporate pressure and flow sensors into soft hydraulic circuit to predict performance of the HHH	AMOLF																												
	Task 3.4	Predicting HHH deformation and actuators performance based on the soft sensory fiber	UTwente																												
	Task 3.5	Build hardware and software to monitor HHH behavior for in vivo and in vitro experiments	Saxion																												
	Task 3.6	Develop cloud software for chronical experiments	Trailblazer																												
	Task 3.7	Develop algorithms and performance indicators to evaluate long-term performance of the HHH	AMOLF, Trailblazer																												
4	**WP4**	**System Integration**	**Saxion MT**																												
	Task 4.1	Elaborate plan for integration and Testing	Saxion, EMC, AMOLF, UT, TU/e, SBMC																												
	Task 4.2	Integration and Testing	Saxion, EMC, AMOLF, UT, TU/e, SBMC																												
	Task 4.3	Evaluation and fine-tuning	Saxion, EMC, UT																												
5	**WP5**	**Proof of concept in large animal model**	**EMC (J. Kluin)**																												
	Task 5.1	Design of in vivo studies, ethics and regulatory requirements	EMC, Medanex																												
	Task 5.2	In vivo testing of heart valves in sheep	EMC, TU/e																												
	Task 5.3	Acute In vivo implantations in large animals from prototype to design freeze	EMC, Partners WP1-4																												
	Task 5.4	Chronic In vivo implantations in large animals	EMC, Medanex																												
6	**WP6**	**Business strategy, regulatory approval & knowledge dissemination**	**EMC (K.M. Veen)**																												
	Task 6.1	Technical dossier filing according to current regulations	EMC, EVOS																												
	Task 6.2	Business strategy development and sustainable financing	EMC, EVOS, DCVA																												
	Task 6.3	Intellectual Property management and legal	EMC, EVOS																												
	Task 6.4	Knowledge dissemination and communication	Streefland, DCVA, EMC, NHS, Harteraad, PHA																												